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AIR FORCE HEALTH STUDY COMPREHENSIVE REPORT

*An Epidemiologic Investigation of
Health Effects in Air Force Personnel
Following Exposure to Herbicides*

February 1984 to March 2005

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Prepared for the
United States Air Force
by
Science Applications International Corporation

2 November 2005

Contract Number: F41624-01-C-1012
SAIC Project Number: 01-0813-04-2273

PREFACE

The Air Force Health Study (AFHS) is an epidemiologic study to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides, with specific emphasis on Agent Orange. This report is a summary of the results of the six physical examinations conducted during the AFHS that began in 1982. Study results have been published in reports for each examination and also have been summarized in articles published in peer-reviewed scientific journals. This report is based on the journal articles and the seven reports published from these six examinations: the Baseline Morbidity Study Results (24 February 1984, referred to as the 1982 baseline examination in this report), the Air Force Health Study First Followup Examination Results (15 July 1987), the Air Force Health Study 1987 Followup Examination Results (16 January 1990), the Air Force Health Study Serum Dioxin Analysis of 1987 Examination Results (7 February 1991), the Air Force Health Study 1992 Followup Examination Results (2 May 1995), the Air Force Health Study 1997 Follow-up Examination Results (22 February 2000), and the Air Force Health Study 2002 Follow-up Examination Results (31 March 2005).

The findings in the articles may differ from the physical examination reports because they may (a) combine data from two or more physical examinations, (b) use different methods of analysis, (c) focus on specific health endpoints, and (d) include different risk factors. The results in the journal articles are often consistent, but sometimes lead to conclusions that differ from the seven reports. For example, published articles on diabetes in Ranch Hand veterans revealed an association with dioxin exposure consistent with the examination report. Published articles on peripheral neuropathy, memory loss, and cancer, however, revealed associations not examined in the examination reports.

This report is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized, with only a brief mention of nonsignificant results. Significant results that appeared consistently across examinations or have biological meaning are emphasized. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis.

The lack of a particular finding does not prove that no association exists and should not lead the reader to conclude that there is no association between herbicide exposure and adverse health. Consistent with the protocol, study investigators continue to question the underlying assumptions of all analyses, explore new ways to analyze data, and collaborate with specialists to determine whether exposure to Agent Orange adversely affected the health of Ranch Hand veterans.

The AFHS is scheduled to end on September 30, 2006.

TABLE OF CONTENTS

PREFACE	I
1 INTRODUCTION.....	1-1
1.1 PURPOSE OF THE REPORT	1-1
1.2 BACKGROUND	1-1
1.3 AIR FORCE HEALTH STUDY DESIGN	1-3
1.4 MORTALITY AND MORBIDITY COMPONENTS	1-3
1.5 TYPES OF DATA COLLECTED	1-4
1.6 AFHS PARTICIPATION	1-5
1.7 REPORT ORGANIZATION	1-5
REFERENCES.....	1-7
2 MEASURES OF EXPOSURE	2-1
2.1 INTRODUCTION	2-1
2.2 GROUP STATUS	2-1
2.3 ORIGINAL AFHS EXPOSURE INDEX	2-2
2.4 SERUM DIOXIN MEASUREMENT	2-3
2.4.1 Initial Dioxin Model	2-4
2.4.2 Categorized Dioxin Model	2-5
2.4.3 1987 Dioxin Model	2-6
2.5 THE ORIGINAL AFHS EXPOSURE INDEX VERSUS SERUM DIOXIN MEASUREMENTS.....	2-7
REFERENCES.....	2-9
3 INTERPRETIVE CONSIDERATIONS	3-1
3.1 INTRODUCTION	3-1
3.2 STUDY DESIGN AND MODELING CONSIDERATIONS	3-1
3.3 INFORMATION BIAS.....	3-2
3.4 CONSISTENCY OF RESULTS.....	3-2
3.5 STRENGTH OF ASSOCIATION	3-3
3.6 RESULTS BASED ON INDIRECT MEASURES OF THE VIETNAM EXPERIENCE AND HERBICIDE EXPOSURE.....	3-3
3.7 BIOLOGICAL PLAUSIBILITY	3-4
3.8 INTERPRETATION OF NONSIGNIFICANT RESULTS.....	3-4

34	3.9	EXTRAPOLATION TO ARMED FORCES GROUND TROOPS	3-4
35	3.10	CONSIDERATIONS FOR SUMMARIZING RESULTS	3-5
36		REFERENCES.....	3-6
37	4	ILLNESSES PRESUMPTIVELY RECOGNIZED AS AGENT ORANGE-CONNECTED.....	4-1
38	4.1	INTRODUCTION	4-1
39	4.2	ACUTE AND SUBACUTE TRANSIENT PERIPHERAL NEUROPATHY	4-2
40	4.3	CHLORACNE	4-3
41	4.4	CHRONIC LYMPHOCYTIC LEUKEMIA	4-3
42	4.5	HODGKIN’S DISEASE	4-3
43	4.6	MULTIPLE MYELOMA	4-4
44	4.7	NON-HODGKIN’S LYMPHOMA	4-4
45	4.8	PORPHYRIA CUTANEA TARDA (PCT)	4-4
46	4.9	PROSTATE CANCER	4-5
47	4.10	RESPIRATORY CANCERS, INCLUDING CANCERS OF THE LUNG, LARYNX,	
48		TRACHEA, AND BRONCHUS	4-5
49	4.11	SOFT TISSUE SARCOMA (OTHER THAN OSTEOSARCOMA, CHONDROSARCOMA,	
50		KAPOSI’S SARCOMA, OR MESOTHELIOMA).....	4-5
51	4.12	SPINA BIFIDA (IN CHILDREN OF VIETNAM VETERANS) (EXCEPT SPINA	
52		BIFIDA OCCULTA).....	4-6
53	4.13	TYPE 2 DIABETES	4-6
54		REFERENCES.....	4-7
55	5	REPRODUCTIVE OUTCOMES.....	5-1
56	5.1	INTRODUCTION	5-1
57	5.2	1982 BASELINE EXAMINATION	5-1
58	5.2.1	Analysis of Live Birth Outcomes - Update.....	5-2
59	5.3	1992 REPRODUCTIVE OUTCOMES REPORT	5-2
60	5.3.1	AFHS Journal Articles Based on 1992 Reproductive Outcomes Report.....	5-4
61	5.4	CONCLUSION	5-4
62		REFERENCES.....	5-5
63	6	MORTALITY	6-1
64	6.1	INTRODUCTION	6-1
65	6.2	1983 BASELINE MORTALITY STUDY.....	6-2
66	6.3	1984 MORTALITY UPDATE	6-2
67	6.4	1985 MORTALITY UPDATE	6-2

68	6.5	1986 MORTALITY UPDATE	6-3
69	6.6	1989 MORTALITY UPDATE	6-3
70	6.7	1991 MORTALITY UPDATE	6-3
71	6.8	1993 MORTALITY UPDATE	6-4
72	6.9	1994 MORTALITY UPDATE	6-4
73	6.10	1996 MORTALITY UPDATE	6-4
74	6.11	MORTALITY THROUGH 1999.....	6-5
75	REFERENCES.....		6-6
76	7	CARDIOVASCULAR ASSESSMENT	7-1
77	7.1	INTRODUCTION	7-1
78	7.1.1	Chapter Structure	7-2
79	7.2	ESSENTIAL HYPERTENSION	7-4
80	7.3	HEART DISEASE (EXCLUDING ESSENTIAL HYPERTENSION).....	7-4
81	7.4	MYOCARDIAL INFARCTION	7-4
82	7.5	SYSTOLIC BLOOD PRESSURE	7-5
83	7.6	DIASTOLIC BLOOD PRESSURE	7-5
84	7.7	ECG.....	7-5
85	7.7.1	Overall.....	7-5
86	7.7.2	Arrhythmia.....	7-5
87	7.7.3	Evidence of Prior Myocardial Infarction	7-5
88	7.7.4	Bradycardia	7-6
89	7.7.5	Tachycardia.....	7-6
90	7.7.6	Right Bundle Branch Block (RBBB).....	7-6
91	7.7.7	Nonspecific ST- and T-Wave Changes.....	7-6
92	7.7.8	Other Diagnoses.....	7-6
93	7.8	FUNDUSCOPIC EXAMINATION.....	7-6
94	7.9	CAROTID BRUITS.....	7-6
95	7.10	PULSES	7-7
96	7.10.1	All Pulses/Peripheral Pulses.....	7-7
97	7.10.2	Leg Pulses	7-7
98	7.10.3	Femoral Pulses	7-7
99	7.10.4	Popliteal Pulses	7-7
100	7.10.5	Dorsalis Pedis Pulses	7-8
101	7.10.6	Posterior Tibial Pulses	7-8
102	7.11	KIDNEY, URETHRA, AND BLADDER (KUB) X-RAY ABNORMALITIES	7-8
103	7.12	AFHS CARDIOVASCULAR MORTALITY THROUGH 1999.....	7-8
104	7.13	CONCLUSION	7-8
105	REFERENCES.....		7-9

106	8 DERMATOLOGY ASSESSMENT	8-1
107	8.1 INTRODUCTION	8-1
108	8.1.1 Chapter Structure	8-2
109	8.2 ACNE – SELF-REPORTED OCCURRENCE AND DURATION	8-3
110	8.3 ACNEIFORM LESIONS.....	8-3
111	8.4 ACNEIFORM SCARS	8-3
112	8.5 HYPERPIGMENTATION	8-3
113	8.6 OTHER DERMATOLOGIC EVALUATION ABNORMALITIES	8-4
114	8.7 DERMATOLOGY INDEX	8-4
115	8.8 CONCLUSION	8-4
116	REFERENCES.....	8-5
117	9 ENDOCRINOLOGY ASSESSMENT	9-1
118	9.1 INTRODUCTION	9-1
119	9.1.1 Chapter Structure	9-4
120	9.2 DIABETES AND GLUCOSE CONTROL.....	9-5
121	9.2.1 Prevalence of Diabetes.....	9-5
122	9.2.2 Diabetic Control.....	9-6
123	9.2.3 Time to Diabetes Onset.....	9-6
124	9.2.4 Fasting Glucose.....	9-6
125	9.2.5 2-hour Postprandial Glucose.....	9-7
126	9.2.6 Fasting Urinary Glucose	9-7
127	9.2.7 2-hour Postprandial Urinary Glucose	9-7
128	9.2.8 Insulin	9-7
129	9.2.9 Hemoglobin A1c.....	9-8
130	9.2.10 C-peptide.....	9-8
131	9.2.11 Glucagon.....	9-9
132	9.2.12 Proinsulin	9-9
133	9.2.13 Diabetes Versus Dioxin Body Burden in Veterans of Operation Ranch Hand.....	9-9
134	9.2.14 Serum Dioxin and Diabetes Mellitus in Veterans of Operation Ranch Hand.....	9-9
135	9.2.15 Letter to the Editor: Weight History, Glucose Intolerance, and Insulin Levels in	
136	Middle-aged Swedish Men	9-10
137	9.2.16 Serum Dioxin, Insulin, Fasting Glucose and Sex Hormone-Binding Globulin in	
138	Veterans of Operation Ranch Hand	9-10
139	9.2.17 Serum Dioxin Level in Relation to Diabetes Mellitus among Air Force Veterans with	
140	Background Levels of Exposure.....	9-10
141	9.2.18 Dioxin and Diabetes Mellitus: An Analysis of the Combined NIOSH and Ranch	
142	Hand Data	9-10
143	9.2.19 Diabetes Mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin Elimination in Veterans of	
144	Operation Ranch Hand.....	9-11
145	9.2.20 Insulin Sensitivity Following Agent Orange Exposure in Vietnam Veterans with	
146	High Blood Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin.....	9-11

147	9.3	THYROID.....	9-11
148	9.3.1	Thyroid Disease	9-11
149	9.3.2	Anti-thyroid Antibodies	9-12
150	9.3.3	Thyroid-stimulating Hormone (TSH)	9-12
151	9.3.4	Thyroxine (T ₄)	9-12
152	9.3.5	Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Levels and Thyroid Function in	
153		Air Force Veterans of the Vietnam War.....	9-12
154	9.4	HYPOTHALAMIC-PITUITARY-TESTIS AXIS.....	9-12
155	9.4.1	Differential Cortisol	9-12
156	9.4.2	Testicular Examination	9-13
157	9.4.3	Testicular Volume (Minimum and Total)	9-13
158	9.4.4	Total Testosterone.....	9-13
159	9.4.5	Free Testosterone	9-13
160	9.4.6	Estradiol	9-13
161	9.4.7	Follicle-stimulating Hormone (FSH)	9-13
162	9.4.8	Luteinizing Hormone (LH)	9-14
163	9.4.9	Serum Dioxin, Testosterone, and Gonadotropins in Veterans of Operation Ranch Hand...	9-14
164	9.5	CONCLUSION	9-14
165		REFERENCES.....	9-15
166	10	GASTROINTESTINAL ASSESSMENT.....	10-1
167	10.1	INTRODUCTION	10-1
168	10.1.1	Chapter Structure	10-2
169	10.2	HEPATITIS	10-4
170	10.2.1	Uncharacterized Hepatitis (Non-A, Non-B, Non-C).....	10-4
171	10.2.2	Prior Hepatitis B	10-4
172	10.3	LIPIDS	10-4
173	10.3.1	Cholesterol	10-4
174	10.3.2	High-density Lipoprotein (HDL) Cholesterol.....	10-5
175	10.3.3	Cholesterol-HDL Ratio	10-5
176	10.3.4	Triglycerides	10-5
177	10.4	LIVER ENZYMES	10-6
178	10.4.1	Alanine Aminotransferase (ALT)	10-6
179	10.4.2	Aspartate Aminotransferase (AST).....	10-6
180	10.4.3	Gamma Glutamyltransferase (GGT).....	10-7
181	10.4.4	Alkaline Phosphatase	10-7
182	10.4.5	Creatine Phosphokinase	10-8
183	10.4.6	Direct Bilirubin	10-8
184	10.4.7	Lactate Dehydrogenase (LDH)	10-8
185	10.5	OTHER LIVER DISORDERS	10-8
186	10.6	PROTEIN PROFILE.....	10-9
187	10.6.1	α -1-Acid Glycoprotein	10-9
188	10.6.2	α -1-Antitrypsin.....	10-9
189	10.6.3	α -2-Macroglobulin	10-9
190	10.6.4	Albumin	10-9

191	10.6.5 Apolipoprotein B	10-10
192	10.6.6 C3 Complement	10-10
193	10.6.7 C4 Complement	10-10
194	10.6.8 Haptoglobin.....	10-10
195	10.6.9 Prealbumin	10-10
196	10.7 PROTHROMBIN TIME.....	10-10
197	10.8 SKIN BRUISES, PATCHES, OR SENSITIVITY	10-11
198	10.9 STOOL HEMOCCULT	10-11
199	10.10 DIOXIN AND HEPATIC ABNORMALITIES IN VETERANS OF OPERATION	
200	RANCH HAND.....	10-11
201	10.11 CONCLUSION.....	10-11
202	REFERENCES.....	10-12
203	11 GENERAL HEALTH ASSESSMENT	11-1
204	11.1 INTRODUCTION	11-1
205	11.1.1 Chapter Structure	11-1
206	11.2 BODY MASS INDEX/BODY FAT	11-2
207	11.3 SELF-PERCEPTION OF HEALTH.....	11-2
208	11.4 RELATIVE AGE APPEARANCE AS ASSESSED BY A PHYSICIAN.....	11-3
209	11.5 CONCLUSION.....	11-3
210	REFERENCES.....	11-4
211	12 HEMATOLOGY ASSESSMENT.....	12-1
212	12.1 INTRODUCTION	12-1
213	12.1.1 Chapter Structure	12-1
214	12.2 HEMATOCRIT	12-2
215	12.3 HEMOGLOBIN.....	12-3
216	12.4 MEAN CORPUSCULAR HEMOGLOBIN	12-3
217	12.5 MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION	12-3
218	12.6 MEAN CORPUSCULAR VOLUME.....	12-3
219	12.7 PLATELET COUNT	12-3
220	12.8 RBC COUNT	12-4
221	12.9 WBC COUNT.....	12-4
222	12.10 ABSOLUTE BASOPHILS	12-4
223	12.11 ABSOLUTE NEUTROPHILS.....	12-4
224	12.12 RBC MORPHOLOGY	12-5
225	12.13 ERYTHROCYTE SEDIMENTATION RATE	12-5

226	12.14	RELATION OF SERUM 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD)	
227		LEVEL TO HEMATOLOGICAL EXAMINATION RESULTS IN VETERANS OF	
228		OPERATION RANCH HAND	12-5
229	12.15	CONCLUSION	12-5
230	REFERENCES.....		12-6
231	13	IMMUNOLOGY ASSESSMENT	13-1
232	13.1	INTRODUCTION	13-1
233	13.1.1	Chapter Structure	13-3
234	13.2	COMPOSITE SKIN TEST DIAGNOSIS.....	13-4
235	13.3	CD2+ CELLS (TOTAL T CELLS)	13-4
236	13.4	CD3+ CELLS (TOTAL T CELLS)	13-5
237	13.5	CD4+ CELLS (HELPER T CELLS)	13-5
238	13.6	CD5+ CELLS (T-CELL MARKER)	13-5
239	13.7	CD8+ CELLS (SUPPRESSOR CELLS)	13-5
240	13.8	CD4+–CD8+ RATIO	13-5
241	13.9	CD14+ CELLS (MONOCYTES)	13-6
242	13.10	CD16+56+ CELLS (NATURAL KILLER CELLS)	13-6
243	13.11	CD20+ CELLS (B CELLS)	13-6
244	13.12	CD25+ CELLS (ACTIVATION MARKER FOR LYMPHOCYTES)	13-7
245	13.13	HUMAN LEUKOCYTE ANTIGEN (HLA)-DR CELLS	13-7
246	13.14	DOUBLE-LABELED CELLS	13-7
247	13.14.1	CD3- with CD16+56+	13-7
248	13.14.2	CD3+ with CD25+	13-7
249	13.14.3	CD4+ with CD8+	13-7
250	13.14.4	CD5+ with CD20+	13-7
251	13.14.5	CD3+CD4+ Cells (Helper T Cells).....	13-8
252	13.15	ABSOLUTE LYMPHOCYTES	13-8
253	13.16	MAXIMUM PHYTOHEMAGGLUTININ (PHA) NET RESPONSE	13-8
254	13.17	PHA NET RESPONSE	13-8
255	13.18	UNSTIMULATED MIXED LYMPHOCYTE CULTURE (MLC) RESPONSE.....	13-8
256	13.19	NATURAL KILLER CELL ASSAY (NKCA) 50/1 PERCENT RELEASE	13-8
257	13.20	NATURAL KILLER CELL ASSAY WITH INTERLEUKIN-2 (NKCI) 50/1 PERCENT	
258		RELEASE AND NET RESPONSE	13-9
259	13.21	IgA	13-9
260	13.22	IgG	13-9
261	13.23	IgM.....	13-9

262	13.24 LUPUS PANEL	13-10
263	13.24.1 Antinuclear Antibody (ANA) Test	13-10
264	13.24.2 ANA Thyroid Microsomal Antibody.....	13-10
265	13.24.3 Mouse Stomach Kidney (MSK) Anti-smooth Muscle Antibody.....	13-10
266	13.24.4 Rheumatoid Factor.....	13-10
267	13.25 CONCLUSION	13-10
268	REFERENCES.....	13-12
269	14 NEOPLASIA ASSESSMENT	14-1
270	14.1 INTRODUCTION	14-1
271	14.1.1 Chapter Structure	14-3
272	14.2 SKIN NEOPLASMS.....	14-4
273	14.2.1 All Skin Neoplasms	14-4
274	14.2.2 Malignant Skin Neoplasms	14-5
275	14.2.2.1 Basal Cell Carcinoma.....	14-5
276	14.2.2.2 Nonmelanoma	14-6
277	14.2.2.3 Sun Exposure-related Malignant Skin Neoplasm	14-6
278	14.2.2 Benign Skin Neoplasms	14-6
279	14.2.3 Skin Neoplasms of Uncertain Behavior or Unspecified Nature	14-6
280	14.3 SYSTEMIC NEOPLASMS	14-6
281	14.3.1 All Systemic Neoplasms	14-6
282	14.3.2 Malignant Systemic Neoplasms.....	14-7
283	14.3.2.1 Bronchus and Lung	14-7
284	14.3.2.2 Colon and Rectum.....	14-7
285	14.3.2.3 Eye, Ear, Face, Head, and Neck	14-7
286	14.3.2.4 Liver	14-7
287	14.3.2.5 Malignant Systemic Neoplasms of the Penis and Other Male Genital Organs	14-7
288	14.3.2.6 Prostate.....	14-8
289	14.3.2.7 Urinary System.....	14-8
290	14.3.2.8 Carcinoma in Situ (Breast, Digestive Organs, Respiratory, Prostate, Penis and	
291	Other Male Genitals, and Bladder and Other and Nonspecified Urinary).....	14-8
292	14.3.3 Benign Systemic Neoplasms.....	14-8
293	14.3.4 Systemic Neoplasms of Uncertain Behavior or Unspecified Nature	14-8
294	14.4 SKIN AND SYSTEMIC NEOPLASMS	14-8
295	14.4.1 All Skin and Systemic Neoplasms	14-8
296	14.4.2 Malignant Skin and Systemic Neoplasms.....	14-9
297	14.5 PROSTATE-SPECIFIC ANTIGEN (PSA)	14-9
298	14.6 AFHS JOURNAL ARTICLES ON CANCER	14-9
299	14.6.1 Serum Dioxin and Cancer in Veterans of Operation Ranch Hand.....	14-9
300	14.6.2 Cancer in US Air Force Veterans of the Vietnam War.....	14-9
301	14.6.3 Did TCDD Exposure or Service in Southeast Asia Increase the Risk of Cancer in	
302	Air Force Vietnam Veterans Who Did Not Spray Agent Orange?	14-10
303	14.7 CONCLUSION	14-10
304	REFERENCES.....	14-11

305	15 NEUROLOGY ASSESSMENT	15-1
306	15.1 INTRODUCTION	15-1
307	15.1.1 Chapter Structure	15-3
308	15.2 HEREDITARY AND DEGENERATIVE NEUROLOGICAL DISEASE	15-5
309	15.3 INFLAMMATORY NEUROLOGICAL DISEASE	15-5
310	15.4 PERIPHERAL DISORDERS	15-5
311	15.5 OTHER NEUROLOGICAL DISORDERS	15-5
312	15.6 CRANIAL NERVE FUNCTION	15-6
313	15.6.1 Balance/Romberg Sign	15-6
314	15.6.2 Facial Sensation	15-6
315	15.6.3 Smell	15-6
316	15.6.4 Visual Fields	15-6
317	15.6.5 Neck Range of Motion.....	15-6
318	15.6.6 Cranial Nerve Index	15-6
319	15.7 PERIPHERAL NERVE STATUS	15-7
320	15.7.1 Muscle Status	15-7
321	15.7.2 Pinprick	15-7
322	15.7.3 Achilles Reflex.....	15-7
323	15.7.4 Patellar Reflex.....	15-7
324	15.8 POLYNEUROPATHY	15-8
325	15.8.1 Vibrotactile Threshold Measurement of the Great Toes.....	15-8
326	15.8.2 Polyneuropathy Severity Index.....	15-9
327	15.8.3 Polyneuropathy Prevalence Indicator	15-9
328	15.8.4 Multiple Polyneuropathy Index	15-9
329	15.8.5 Confirmed Polyneuropathy Index.....	15-9
330	15.8.6 Serum Dioxin and Peripheral Neuropathy in Veterans of Operation Ranch Hand.....	15-9
331	15.9 CENTRAL NERVOUS SYSTEM (CNS) COORDINATION PROCESSES	15-10
332	15.9.1 Coordination	15-10
333	15.9.2 Gait.....	15-11
334	15.9.3 Tremor.....	15-11
335	15.9.4 CNS Index.....	15-11
336	15.10 CONCLUSION	15-11
337	REFERENCES.....	15-13
338	16 PSYCHOLOGY ASSESSMENT	16-1
339	16.1 INTRODUCTION	16-1
340	16.1.1 Chapter Structure	16-2
341	16.2 ALCOHOL DEPENDENCE	16-3
342	16.3 OTHER NEUROSES.....	16-3
343	16.4 ANGER, ANXIETY, FATIGUE, AND ISOLATION	16-4
344	16.5 SLEEP PROBLEMS.....	16-4

345	16.6	CORNELL INDEX.....	16-5
346	16.7	CORNELL MEDICAL INDEX (CMI)	16-5
347	16.8	MILLON CLINICAL MULTIAXIAL INVENTORY (MCMI).....	16-5
348	16.8.1	Antisocial.....	16-6
349	16.8.2	Avoidant	16-6
350	16.8.3	Compulsive.....	16-6
351	16.8.4	Dependent.....	16-6
352	16.8.5	Histrionic	16-6
353	16.8.6	Narcissistic.....	16-6
354	16.8.7	Passive-aggressive	16-6
355	16.8.8	Schizoid	16-6
356	16.8.9	Borderline	16-7
357	16.8.10	Paranoid	16-7
358	16.8.11	Schizotypal.....	16-7
359	16.8.12	Alcohol Abuse	16-7
360	16.8.13	Anxiety.....	16-7
361	16.8.14	Dysthymia.....	16-7
362	16.8.15	Hypomania.....	16-7
363	16.8.16	Somatoform.....	16-7
364	16.8.17	Psychotic Depression	16-7
365	16.8.18	Serum Dioxin and Psychological Functioning in U.S. Air Force Veterans of the Vietnam War: MCMI	16-7
366			
367	16.9	MINNESOTA MULTIPHASIC PERSONALITY INVENTORY (MMPI).....	16-8
368	16.9.1	Depression	16-8
369	16.9.2	Hypochondria.....	16-8
370	16.9.3	Hysteria.....	16-8
371	16.9.4	Mania/Hypomania.....	16-8
372	16.9.5	Masculinity/Femininity	16-8
373	16.9.6	Paranoia	16-8
374	16.9.7	Schizophrenia.....	16-8
375	16.9.8	Social Introversion.....	16-9
376	16.9.9	Serum Dioxin and Psychological Functioning in U.S. Air Force Veterans of the Vietnam War: MMPI.....	16-9
377			
378	16.10	SYMPTOM CHECKLIST-90-REVISED (SCL-90-R)	16-9
379	16.10.1	Anxiety.....	16-9
380	16.10.2	Depression	16-10
381	16.10.3	Hostility	16-10
382	16.10.4	Obsessive-compulsive Behavior	16-10
383	16.10.5	Paranoid Ideation	16-11
384	16.10.6	Psychoticism	16-11
385	16.10.7	Somatization	16-11
386	16.10.8	Global Severity Index	16-12
387	16.11	SERUM DIOXIN AND COGNITIVE FUNCTIONING IN VETERANS OF	
388		OPERATION RANCH HAND	16-12
389	16.12	CONCLUSION	16-13
390		REFERENCES.....	16-14

391	17 PULMONARY ASSESSMENT	17-1
392	17.1 INTRODUCTION	17-1
393	17.1.1 Chapter Structure	17-1
394	17.2 ASTHMA.....	17-3
395	17.3 BRONCHITIS.....	17-3
396	17.4 PLEURISY	17-3
397	17.5 PNEUMONIA.....	17-3
398	17.6 THORAX AND LUNG ABNORMALITY	17-3
399	17.7 HYPERRESONANCE.....	17-3
400	17.8 RALES	17-3
401	17.9 WHEEZES.....	17-3
402	17.10 X-RAY INTERPRETATION	17-4
403	17.11 FEV ₁	17-4
404	17.12 FVC.....	17-4
405	17.13 RATIO OF OBSERVED FEV ₁ TO OBSERVED FVC	17-4
406	17.14 LOSS OF VITAL CAPACITY	17-4
407	17.15 OBSTRUCTIVE ABNORMALITY.....	17-4
408	17.16 CONCLUSION.....	17-5
409	REFERENCES.....	17-6
410	18 RENAL ASSESSMENT	18-1
411	18.1 INTRODUCTION	18-1
412	18.1.1 Chapter Structure	18-1
413	18.2 HISTORY OF KIDNEY DISEASE.....	18-2
414	18.3 SERUM CREATININE.....	18-2
415	18.4 URINARY OCCULT BLOOD.....	18-2
416	18.5 URINARY WHITE BLOOD CELLS.....	18-3
417	18.6 URINARY PROTEIN.....	18-3
418	18.7 URINE SPECIFIC GRAVITY	18-3
419	18.8 CONCLUSION	18-3
420	REFERENCES.....	18-4
421	19 CONCLUSION	19-1
422	REFERENCES.....	19-5
423	APPENDIX: ABBREVIATIONS AND ACRONYMS	

1 INTRODUCTION

This chapter describes the purpose and background of the Air Force Health Study (AFHS) and provides an overview of the study design and format of this report.

1.1 PURPOSE OF THE REPORT

The objective of the AFHS was to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides, with specific emphasis on Agent Orange, a one-to-one mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). In this report, the use of the term “dioxin” refers to TCDD. The principal investigators and the AFHS reports used dioxin levels as a surrogate for exposure for most of the study, as derived from the early peer review groups, review of the literature, and the Ranch Hand Advisory Committee. Although there are approximately 75 different congeners of dioxin, TCDD is believed to be the most toxic and the only contaminant of 2,4,5-T.

This report is a discussion and a compilation of the findings from research related to the mortality, reproductive outcomes, and morbidity components of the AFHS. Subsequent to the protocol, which was published in 1982 (1), the baseline physical examination was conducted in 1982, and follow-up examinations were performed in 1985, 1987, 1992, 1997, and 2002. Reports and journal articles describing the findings of each of these examinations have been published (2-8).

1.2 BACKGROUND

In 1961, President Ngo Dinh Diem of South Vietnam asked the United States to conduct aerial spraying of herbicides in his country. In November 1961, President John F. Kennedy approved the use of herbicides, but only as a limited experiment (9). In January 1962, Operation Ranch Hand, the designation for the program, began for the purpose of defoliation and crop destruction in support of tactical military operations in the Republic of Vietnam (RVN). Gradually, limitations were relaxed and spraying became more frequent (9). Operation Ranch Hand dispersed approximately 19 million gallons of herbicides on an estimated 10 to 20 percent of the RVN from 1962 to 1971. The herbicides sprayed were code-named Herbicide Green, Herbicide Pink, Herbicide Purple, Herbicide Orange, Herbicide White, and Herbicide Blue. 2,4,5-T was an active ingredient in Herbicides Green, Pink, Purple, and Orange, and dioxin was produced as an inadvertent contaminant of 2,4,5-T during the manufacturing process. 2,4-D was an active ingredient in Herbicides Purple, Orange, and White. Picloram was an active ingredient in Herbicide White; cacodylic acid was the active ingredient in Herbicide Blue. Of the 19 million gallons of herbicide dispersed, approximately 11 million gallons were Herbicide Orange, also called “Agent Orange,” the primary defoliant of the six herbicides used in the program (9, 10).

The following chart lists the names, periods of use, and compositions of the major herbicide mixtures used in the RVN (9):

Military Color Code or Trade Name*	Period of Use	Composition (Active Ingredient)
Pink	1962-1964	60% n-butyl ester of 2,4,5-T, 40% isobutyl ester of 2,4,5-T
Green	1962-1964	100% n-butyl ester of 2,4,5-T
Pink-green mixture	1962-1964	80% n-butyl ester of 2,4,5-T, 20% isobutyl ester of 2,4,5-T
Dinoxol	1962-1964	50% butyoxoethanol ester of 2,4-D, 50% butyoxoethanol ester of 2,4,5-T
Trinoxol	1962-1964	100% butyoxoethanol ester of 2,4,5-T
Purple	1962-1964	50% n-butyl ester of 2,4-D, 30% n-butyl ester of 2,4,5-T, 20% isobutyl ester of 2,4,5-T
Blue	1962-1971	100% sodium salt of cacodylic acid
Orange	1965-1970	50% n-butyl ester of 2,4-D, 50% n-butyl ester of 2,4,5-T
Orange II	1965-1970	50% n-butyl ester of 2,4-D, 50% isooctyl ester of 2,4,5-T
White	1965-1971	80% triisopropanolamine salt of 2,4-D, 20% triisopropanolamine salt of picloram

*Herbicide drums were identified by a circular band of paint colored in correspondence with these color codes.

From the start, Operation Ranch Hand was heavily scrutinized because of the controversial nature of the program and the political sensitivity to charges of chemical warfare contained in enemy propaganda. The concerns were initially based on military, political, and ecological issues, but shifted to the issue of health in 1970. The primary concern in the controversy over the human health effects of these herbicides was related to dioxin, a component in four of the six herbicides sprayed. The Air Force estimated that 368 pounds of dioxin were released over 6 million acres in the RVN (10). Other researchers have estimated that the amount of dioxin released was nearly double the Air Force estimate (11). Claims of exposure to herbicides, particularly to Agent Orange, and perceived adverse health effects among U.S. military service personnel resulted in substantial controversy and, eventually, class-action litigation. Social concern for the Agent Orange issue continues to be reflected in scientific research, media presentations, congressional hearings, and legal action.

Since 1970, governmental agencies, universities, and industrial firms have funded numerous human and animal studies of dioxin effects. A key scientific issue in these studies was the degree of exposure (e.g., who was exposed and to what extent each individual was exposed). Unfortunately, in many of the human studies, population identification and exposure estimation were scientifically elusive.

In October 1978, the Air Force Deputy Surgeon General made a commitment to Congress and the White House to conduct a health study on the Operation Ranch Hand population. This population comprised the aviators and ground support crews who disseminated the majority of the defoliants in the RVN. The Surgeon General tasked the U.S. Air Force School of Aerospace Medicine at Brooks Air Force Base, Texas, to develop a study protocol. In 1982, after extensive peer review, the study protocol was published (1) and the epidemiological study began. The now Brooks City-Base organizations responsible for executing the protocol have been reorganized and renamed several times since 1982. Currently, the Air Force Research Laboratory, Human Effectiveness Directorate, is responsible for the technical aspects of the study, and the Human Systems Group, Agile Combat Support Systems Wing, is responsible for program management.

In 1987, when the serum dioxin assay became available, the Air Force entered into a collaborative effort with the Centers for Disease Control and Prevention (CDC) to measure the serum dioxin levels in the AFHS population. The results of that effort demonstrated that substantially elevated levels of dioxin

could still be found in the serum of some Ranch Hands (12, 13). Studies of serum dioxin levels have suggested that of all the military personnel who served in the RVN, the Ranch Hand cohort was one of the most highly exposed to herbicides containing dioxin (14). If herbicides caused an adverse health effect, then, based on the principle of dose-response, the Ranch Hands should have manifested more or earlier evidence of adverse health.

1.3 AIR FORCE HEALTH STUDY DESIGN

For the baseline examination, the population ascertainment process identified 1,264 Ranch Hand personnel who served in Southeast Asia (SEA) between 1962 and 1971. At the beginning of the AFHS, a Comparison group was identified. Comparison veterans flew primarily transport missions in SEA during the same time period that the Ranch Hand unit was active. Their units used C-130 transport planes flown and serviced by crews with similar training and background as those of Ranch Hand veterans. While Ranch Hand veterans spent most of their SEA service in the RVN, Comparison veterans spent on average less than 30 percent of their SEA service in the RVN and were stationed mostly in Taiwan, the Philippines, Guam, Japan, and Thailand. These Comparison veterans may have been stationed in one, but usually in at least two countries; many had repeated tours of duty in the region. A computerized selection procedure was used to identify Comparisons with similar characteristics to each Ranch Hand veteran.

Comparisons were matched to a Ranch Hand, based on age, race, and military occupation (officer-pilot, officer-navigator, officer-other, enlisted flyer, enlisted groundcrew). As many as 10 Comparisons were identified for each Ranch Hand. The purpose of identifying multiple Comparisons was an attempt to maintain the size of the Comparison group when a previously chosen Comparison declined to participate in a subsequent follow-up examination. Ranch Hands could not be replaced because the entire population was asked to participate. Comparisons, however, could be replaced. A protocol was established to describe the circumstances under which a Comparison was replaced and the method for replacement of Comparisons. After a personnel records review, an average of eight Comparison subjects were matched to each Ranch Hand.

1.4 MORTALITY AND MORBIDITY COMPONENTS

The mortality component addressed noncombat mortality from the time of the SEA assignment. A baseline mortality review was conducted in 1982, and the mortality follow-up reports included periodic mortality updates over the course of the AFHS. For the baseline mortality review and the first four updates, five individuals were randomly selected from the matched Comparison set for each Ranch Hand for a 1:5 design. In 1987, the design was expanded to include all 19,078 veterans in the Comparison population.

The baseline morbidity component, begun in 1982, reconstructed the medical history of each participant by reviewing and coding past medical records. A cross-sectional element, designed to assess the participant's current state of physical and mental health, was based on comprehensive physical examinations and questionnaires. Information on reproductive outcomes also was collected. For the morbidity component of the study, each living Ranch Hand and a random living member of his Comparison set were selected to participate in the examination. The morbidity follow-up examinations comprised sequential questionnaires, medical records reviews, and physical examinations in 1985, 1987, 1992, 1997, and 2002. Participation was voluntary and each participant signed an informed consent form at the examination site.

For the baseline examination and the 1985 and 1987 follow-up examinations, the major focus of the analyses was to compare the health status of the Ranch Hands (i.e., the exposed cohort) with that of the Comparisons (i.e., the unexposed cohort). Methodology to measure dioxin body burden in blood was not made available until February 1987. During the 1987 physical examination, the Air Force began a collaborative study with the CDC to measure dioxin levels in the serum of Ranch Hands and Comparisons (12, 13, 15). The measurement of serum dioxin levels led to a statistical evaluation to assess dose-response relations between dioxin and health endpoints in 12 clinical areas. This was the first large-scale study of dose-response effects based on a direct measurement of dioxin. The statistical analyses associated with the serum data evaluated the association between a specified health endpoint and dioxin among the Ranch Hands. The analyses also contrasted the health of various categories of Ranch Hands having differing serum dioxin levels with the health of Comparisons having background levels (10 parts per trillion or less) of serum dioxin (5). The analysis of dose-response relations based on serum assays provided an important enhancement to the previous AFHS investigations.

In 1992, the fourth examination was initiated. The analysis focused on group differences between the Ranch Hand and Comparison cohorts and on the association of each health endpoint with serum dioxin levels. The fifth examination began in 1997, and the sixth and final examination began in 2002. As in 1992, the analyses in 1997 and 2002 focused on group differences between the Ranch Hand and Comparison cohorts and on the association of each health endpoint with extrapolated initial and 1987 serum dioxin levels (described in Chapter 2).

1.5 TYPES OF DATA COLLECTED

The types of data collected on participants included questionnaire data, medical records, physical examination and laboratory findings, and biological specimens. A baseline questionnaire was developed in 1982 and the questions remained the same for all six examinations. This questionnaire obtained information on demographics, education, occupation, medical history, study compliance, toxic exposures, and reproductive history. In general, responses to histories and other questions where the response did not change over time were obtained in the baseline questionnaire. All veterans who participated in the 1982 baseline examination completed the baseline questionnaire at that time, and a veteran who was new to the AFHS after 1982 completed the baseline questionnaire when he first participated in the study.

In examinations subsequent to the baseline examination, all participants were asked questions to update their histories since their last interviews. These data were obtained and recorded in an interval questionnaire. Reported health conditions in the baseline and interval questionnaires were confirmed by a review of external medical records and classified using International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes.

The core content of the interval questionnaire has remained constant since its inception with only minor modifications. If a veteran participated in the AFHS for the first time in a follow-up examination (1985, 1987, 1992, 1997, or 2002), he was administered a baseline questionnaire to collect historical information through 1982 and an interval questionnaire to collect updates since 1982. Administering a baseline questionnaire at the first time of participation in the study and collecting interval updates when a participant attended a follow-up examination allowed the Air Force to gather histories without unnecessary repetition.

The physical examination portion included laboratory testing, physical examinations, psychological testing, medical debriefings, and specialized testing (e.g., nerve conduction velocity testing at the 2002 physical examination). The Air Force carefully prescribed the details of the examination in an examiner's

handbook, given to each of the examining clinicians. Clinical variations were neither desired nor authorized; all proposed examination procedural changes were reviewed in detail by Air Force technical and contractual personnel prior to the start of the examinations. An important objective of the entire physical examination process was to ensure that bias was not created by any procedural change.

The requirement for the clinic staff to be “blinded” to the participant’s group status (i.e., Ranch Hand, Comparison) was particularly stringent. The clinical staff was prohibited from knowing or seeking information as to the group identity of any participant. Participants also were instructed not to divulge their group status to any of the staff members. At the end of his examination, each participant was asked to note on the evaluation form whether such information was sought by any member of the clinical or paramedical staff. If necessary, but only rarely, the physician or technician involved was reminded to be more careful in his or her conversations.

The examination content, as designed by the Air Force, emphasized detection of medical endpoints suspected of being associated with exposure to phenoxy herbicides, chlorophenols, or dioxin. In each follow-up examination, the Air Force used findings from the previous examination to refine the next examination.

1.6 AFHS PARTICIPATION

Across the 25 years of examinations, participation in the AFHS has been considered excellent for a cohort of this size and age. The number of Ranch Hands and Comparisons who participated in each of the six examinations is provided below.

Group/Examination	1982	1985	1987	1992	1997	2002
Eligible to Participate	1,209	1,199	1,188	1,149	1,102	1,043
Ranch Hand Participants	1,046	1,017	996	953	870	777
Percentage of Ranch Hands Who Participated Relative to Those Eligible to Participate	86.5%	84.8%	83.8%	82.9%	78.9%	74.5%
Comparison Participants	1,223	1,292	1,298	1,280	1,251	1,174
Total	2,269	2,309	2,294	2,233	2,121	1,951

Of the 1,043 Ranch Hands who were eligible to participate in the 2002 follow-up examination, 777 chose to participate (74.5%). Of the 777 Ranch Hands and 1,174 Comparisons who participated in the 2002 follow-up examination, 671 (86.4%) of the Ranch Hands and 811 (69.0%) of the Comparisons participated in all six examinations.

1.7 REPORT ORGANIZATION

This report is organized as follows:

- Chapter 1 (Introduction) explains the purpose of the report; provides summary background information on the AFHS; describes the study design; and discusses mortality and morbidity components, the types of data collected, statistics on AFHS participation, and the organization of this report.
- Chapter 2 (Measures of Exposure) describes the three basic methods for quantifying exposure to herbicides and dioxin that have been used across the history of the AFHS.

- Chapter 3 (Interpretive Considerations) discusses specific technical items and issues that may have affected the interpretations of results found in the AFHS reports and journal articles.
- Chapter 4 (Illnesses Presumptively Recognized as Agent Orange-Connected) describes findings in the AFHS population that correspond to the 12 conditions that the Department of Veterans Affairs presumed were related to exposure to herbicides, such as Agent Orange, among veterans serving in-country during the Vietnam War.
- Chapter 5 (Reproductive Outcomes) describes findings from reports and journal articles that study the health, survival, and reproductive outcomes of Ranch Hands.
- Chapter 6 (Mortality) presents the results of analyses on the cumulative all-cause and individual-cause mortality of Ranch Hands.
- Chapters 7 through 18 present a summary of results found in the statistical analyses that were conducted on morbidity data collected from the 1982, 1985, 1987, 1992, 1997, and 2002 examinations. These chapters are organized by clinical area and further organized by health endpoint. The chapters corresponding to the 12 clinical areas are as follows:
 - Chapter 7: Cardiovascular Assessment
 - Chapter 8: Dermatology Assessment
 - Chapter 9: Endocrinology Assessment
 - Chapter 10: Gastrointestinal Assessment
 - Chapter 11: General Health Assessment
 - Chapter 12: Hematology Assessment
 - Chapter 13: Immunology Assessment
 - Chapter 14: Neoplasia Assessment
 - Chapter 15: Neurology Assessment
 - Chapter 16: Psychology Assessment
 - Chapter 17: Pulmonary Assessment
 - Chapter 18: Renal Assessment.
- Chapter 19 (Conclusions) provides an overall summary of the reproductive outcomes, mortality, and morbidity findings.

This report is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized, with only a brief mention of nonsignificant results. Significant results that appeared consistently across examinations or have biological meaning are emphasized. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis.

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2 MEASURES OF EXPOSURE

2.1 INTRODUCTION

Throughout the 25 years of the Air Force Health Study (AFHS), numerous techniques have been used in attempts to quantify exposure to herbicides. The classic method of comparing “exposed” and “unexposed” veterans have been termed “Group” analyses in the AFHS and have been used in analyses of data from the baseline and all follow-up examinations. By the nature of this two-category classification, however, the magnitude of exposure within the exposed group was not quantified. In the reports based on data collected at the 1982, 1985, and 1987 examinations, an exposure index was constructed based on personnel records and spraying history. During the 1987 physical examination, as the analytical technology became available, the Air Force began a collaborative study with the Centers for Disease Control and Prevention (CDC) to measure dioxin levels directly in the serum of Ranch Hands and Comparisons (1-3). Data collected at the 1987, 1992, 1997, and 2002 follow-up examinations were analyzed using the serum dioxin measurement.

A summary of the measures of exposure used to analyze data from each examination is shown below:

Measure of Exposure/Examination	1982	1985	1987	1992	1997	2002
Group	X	X	X	X	X	X
Exposure Index	X	X	X			
Serum Dioxin Measurement			X	X	X	X

None of these methods is without controversy, and all methods have their advantages and disadvantages. A background and discussion of these three methods are provided in more detail in this chapter. These methods of measuring exposure were used in analyzing mortality, reproductive outcome, and morbidity data, and the subsequent chapters of this report summarize the findings from the analysis.

2.2 GROUP STATUS

The exposed population, termed “Ranch Hand,” was defined as those individuals who were formally assigned to the U.S. Air Force organizations responsible for the aerial dissemination of herbicides and insecticides with C-123 aircraft on the Republic of Vietnam (RVN) from 1962 through 1971. These individuals were identified from historical data sources (morning reports, military personnel records, and historical computer tapes) at the National Personnel Records Center, St. Louis, Missouri, and the U.S. Air Force Human Resources Laboratory, Brooks Air Force Base, Texas.

A review of all specialized flight units present in Southeast Asia (SEA) during the Vietnam War revealed that there did not exist an absolutely ideal control group for the Ranch Hand population. Non-Ranch Hand crews flying C-123 aircraft were considered as a comparison group, but the limited size of this population and the subsequent reconfiguration of these aircraft for transport and insecticide missions raised the possibility that a control group from this population might not truly be unexposed. Crewmembers of C-7 aircraft were considered, but the size of this population also was limited and these crewmembers served in the RVN after 1967 only. It finally was decided to use C-130 crewmembers as the control group.

The Comparison population was defined as those individuals who were assigned to C-130 aircraft organizations in SEA during the same time period as the Ranch Hands. Cargo-mission aircrew members and support personnel were selected because of sufficient population size and similar training and military background experiences to the Ranch Hand group. The Comparison population was not engaged in the aerial spraying of herbicides or insecticides. Identification of this population was completed using similar methods to those used for the Ranch Hand group.

Ranch Hands and multiple Comparisons were matched by closest month of birth, race (Black versus non-Black), and occupational code (categorized as officer-pilot, officer-navigator, officer-other, enlisted-flying, and enlisted-ground). Matching Ranch Hands and Comparisons on age attempted to account for the many clinical symptoms and signs associated with advancing age. Matching on race attempted to account for differences in chronic disease development. Military occupation was strongly associated with educational background and socioeconomic status.

As many as 10 Comparisons were identified for each Ranch Hand. The purpose of identifying multiple Comparisons was an attempt to maintain the size of the Comparison group when a previously chosen Comparison declined to participate in a subsequent follow-up examination. A declining study group size lessens the ability to detect a statistical difference between Ranch Hands and Comparisons. Ranch Hands could not be replaced because the entire population was asked to participate. Comparisons, however, could be replaced. A protocol was established to describe the circumstances under which a Comparison was replaced and the method for replacement.

Analyses contrasting the Ranch Hand and Comparison cohort are straightforward, easy to interpret, and well established in epidemiological studies when a better measure of exposure is not available. Ranch Hands were coded as “exposed” in these analyses, and Comparisons were coded as “not exposed,” without regard to the magnitude of the exposure or possible misclassifications.

Results of the dioxin assay, which are discussed in more detail later in this chapter, appeared to show a difference in measured dioxin levels among the three military occupational categories (officers, enlisted flyers, and enlisted groundcrew). As an attempt to quantify exposure, three contrasts of Ranch Hands and Comparisons were performed along with the overall Ranch Hand versus Comparison contrast for the reports on the 1992, 1997, and 2002 follow-up examinations. These contrasts compared Ranch Hands and Comparisons within the three military occupational categories. As discussed below, the median levels of exposure to dioxin among Ranch Hands were highest for enlisted groundcrew, followed by enlisted flyers, then officers.

2.3 ORIGINAL AFHS EXPOSURE INDEX

The exposure index as originally described in the AFHS protocol was used for the analysis of data collected at the 1982 baseline, 1985 follow-up, and 1987 follow-up examinations. The exposure index was related to the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-containing herbicides: Herbicide Orange, Herbicide Purple, Herbicide Pink, and Herbicide Green. Archived samples of Herbicide Purple suggested that the material had a mean TCDD concentration of approximately 33 parts per million (ppm) and Herbicide Orange had a mean concentration of 2 ppm. Herbicides Pink and Green contained twice the TCDD of Herbicide Purple and, therefore, have been estimated to contain TCDD at a concentration of approximately 66 ppm (4, 5).

The exposure index used, E_i , specific to each Ranch Hand subject i , was $E_i = W * G_i / N_i$, where

W = TCDD weighting factor

G_i = gallons of TCDD-containing herbicide sprayed in the RVN theater during the i^{th} subject's tour of duty, and

N_i = number of airmen with subject's duties in the Vietnam theater during the i^{th} subject's tour of duty.

The exposure index was, therefore, directly related to the amount of TCDD-containing herbicide sprayed and inversely related to the number of airmen with similar duties.

The TCDD weighting factor was 24 or 1, depending on whether the material sprayed was sprayed before or after 1 July 1965. The weighting factor of 1 was used for the period after 1 July 1965, as documentation showed that only Herbicide Orange was disseminated by Air Force-flown, fixed-wing aircraft at that time. Prior to 1 July 1965, a combination of Herbicides Green, Pink, and Purple were sprayed by Air Force personnel in the RVN. After analysis of the data and normalization to Agent Orange concentrations, a weighting factor of 24 was established. Herbicides Blue and White also were sprayed during these time periods, but these herbicides did not contain TCDD and, therefore, were not used in determining a TCDD weighting factor.

The dates of each subject's tour(s) of duty in the RVN were determined by a review of military records. Records and reports were used to construct a table of gallons of TCDD-containing herbicide sprayed for each month during Operation Ranch Hand. Only fixed-wing spray missions were used because Ranch Hand personnel were not involved with helicopter and other spraying, such as from a backpack. The tour dates and the amount sprayed were combined to determine the gallons of TCDD-containing herbicide sprayed in the RVN theater during the i^{th} subject's tour of duty.

The number of Ranch Hand airmen with the subject's duties in the Vietnam theater during the i^{th} subject's tour of duty was determined relative to the five military occupational categories: officer-pilot, officer-navigator, officer-other, enlisted-flying, and enlisted-ground. For the purposes of analysis, the first three categories were combined into a single class called "officers." Navigators and pilots were exposed in the same manner, and other officers were administrators whose exposure was considered effectively zero. In addition, all administrative personnel in the enlisted ground category were assigned a zero exposure value. The number of Ranch Hand airmen in each of the three categories—officer, enlisted-flying, and enlisted-ground—was used in the calculation of the exposure index.

2.4 SERUM DIOXIN MEASUREMENT

At the 1987 physical examination, the Air Force initiated a collaborative study with the CDC to measure dioxin levels in the serum of Ranch Hands and Comparisons (1-3). The results of that effort demonstrated that substantially elevated levels of dioxin could still be found in the serum of some Ranch Hands (1, 2). Studies of serum dioxin levels have suggested that of all the military personnel who served in the RVN, the Ranch Hand cohort was one of the most highly exposed to herbicides. If dioxin caused an adverse health effect, then, based on the principle of dose-response, the Ranch Hands should have manifested more or earlier evidence of adverse health.

The analysis of dose-response relations based on serum assays provided an important enhancement to the previous AFHS investigations. This was the first large-scale study of dose-response effects based on a direct measurement of dioxin.

At the 1992, 1997, and 2002 follow-up examinations, attempts were made to determine dioxin levels for new subjects and those who were not previously measured at the 1987 follow-up examination. In addition, serum samples were taken from selected Ranch Hands at these examinations to provide insight on dioxin levels and the elimination of dioxin from the body.

The measurement of serum dioxin levels led to a statistical evaluation that assessed dose-response relations between dioxin and health endpoints in 12 clinical areas. The statistical analyses associated with the serum data evaluated the association between a specified health endpoint and dioxin among the Ranch Hands. The analyses also contrasted the health of various categories of Ranch Hands having differing serum dioxin levels with the health of Comparisons having background levels (10 parts per trillion [ppt] or less) of serum dioxin (6). In particular, three forms of the measure of dioxin were used, referred to as initial dioxin, categorized dioxin, and 1987 dioxin.

The correlation between the original AFHS exposure index and serum dioxin levels was described in the dioxin analysis of the 1987 physical examination results (6). The exposure index was an indirectly calculated measure derived solely from personnel records and historical information. The serum dioxin level was used as a measure of exposure, and dioxin levels in Ranch Hands appeared to be placed logically relative to cohorts from other dioxin studies. In general, the relation between the measures of dioxin and the original AFHS exposure index showed weak associations between these alternative measures of exposure. The analysis reflected the high percentage of veterans who would be misclassified with regard to dioxin level if the original AFHS exposure index was assumed as the standard. For example, 77 of 287 (26.8%) Ranch Hand veterans in the original AFHS high exposure index category had dioxin levels less than 9 ppt.

2.4.1 Initial Dioxin Model

The relation between a health endpoint and an extrapolated initial dioxin measure was examined for Ranch Hands who had a 1987 dioxin measurement greater than 10 ppt. Data on 213 Ranch Hand veterans with dioxin measured in blood collected in 1982, 1987, 1992, and 1997 produced a half-life estimate of 7.6 years (7); this estimate was used to extrapolate the 1987 dioxin level back in time to the end of the tour of duty that qualified a Ranch Hand veteran for inclusion in this study. If a Ranch Hand did not have a 1987 dioxin level, then the first dioxin measured, either at the 1992, 1997, or 2002 physical examination, was used to estimate the initial dioxin level. A statistical adjustment for body mass index at the time of the participant's blood measurement of dioxin was included in this model to account for body mass index-related differences in elimination rate (7).

Regardless of when the dioxin was measured, Ranch Hand veterans with a level less than or equal to 10 ppt were excluded from statistical analyses. Pharmacokinetic studies (7) were restricted to 343 Ranch Hand veterans with 1987 dioxin greater than 10 ppt because it was thought this value represented an upper threshold for background exposure (as evidenced by the fact that 10 ppt was the 98th percentile of the Comparison dioxin distribution) and that the ability to extrapolate using the half-life estimate did not hold at background levels.

2.4.2 Categorized Dioxin Model

The Ranch Hands for whom an initial dioxin was estimated were divided into two categories based on their initial dioxin measures. These two categories were referred to as “low Ranch Hand” and “high Ranch Hand.” Two additional categories—Ranch Hands with serum dioxin levels at or below 10 ppt and Comparisons—were formed and included in the model. Ranch Hands with serum dioxin levels at or below 10 ppt were assigned to the “background Ranch Hand” category. If a Ranch Hand did not have a 1987 dioxin measurement, the first measured dioxin level was used. Another category was examined by combining the low and high Ranch Hand categories.

Consequently, five categories were used in categorized dioxin analyses:

- Comparisons
- Background Ranch Hands (serum dioxin levels at or below 10 ppt)
- Low Ranch Hands (serum dioxin levels greater than 10 ppt, category cutpoint based on initial dioxin level but varied by examination, cutpoint specified in the table below)
- High Ranch Hands (serum dioxin levels greater than 10 ppt, category cutpoint based on initial dioxin level but varied by examination, cutpoint specified in the table below)
- Low and high Ranch Hands combined (serum dioxin levels greater than 10 ppt, all Ranch Hands included).

The relation between the health endpoint in each of the four Ranch Hand categories and the health endpoint in the Comparison category was examined. As with analyses involving initial dioxin, a statistical adjustment for body mass index at the time of the participant’s blood measurement of dioxin was included in this model (7).

Whereas the extrapolated initial dioxin measure used dioxin in its continuous form for analysis, categorized dioxin inherently placed a participant in one of the five classifications provided above. Since 1987, the methodology has been refined, the estimate of the half-life has been revised using additional data, the cohorts attending the follow-up examination have changed, and the nomenclature of the categories has changed. Below is a list of which participants are included in each of the dioxin categories for analysis of the 1987, 1992, 1997, and 2002 follow-up examinations:

Dioxin Category	1987 Follow-up Examination	1992 Follow-up Examination	1997 Follow-up Examination	2002 Follow-up Examination
Comparison	≤10 ppt measured dioxin level*	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level	All
Background (Ranch Hands)	≤10 ppt measured dioxin level**	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level	≤10 ppt measured dioxin level
Low (Ranch Hands)	15 ppt<measured dioxin level≤33 ppt	measured dioxin level>10 ppt, initial dioxin≤143 ppt	measured dioxin level>10 ppt, initial dioxin≤94 ppt	measured dioxin level>10 ppt, initial dioxin≤118 ppt
High (Ranch Hands)	measured dioxin level>33 ppt	measured dioxin level>10 ppt, initial dioxin>143 ppt	measured dioxin level>10 ppt, initial dioxin>94 ppt	measured dioxin level>10 ppt, initial dioxin>118 ppt
Low and High (Ranch Hands)	measured dioxin level>15 ppt	measured dioxin level>10 ppt	measured dioxin level>10 ppt	measured dioxin level>10 ppt

*called “Background” in the 1987 follow-up examination report

**called “Unknown” in the 1987 follow-up examination report

2.4.3 1987 Dioxin Model

The relation between the health endpoint and dioxin levels, as measured in 1987, was examined for all Ranch Hands with a dioxin measurement. If a Ranch Hand did not have a 1987 dioxin measurement, the first dioxin level obtained, either in 1992, 1997, or 2002, was extrapolated to the date of the 1987 physical examination. If the first dioxin level was not obtained in 1987 and was less than or equal to 10 ppt, it was not extrapolated to 1987 level, but used at the measured value. This measure was termed “current dioxin” in the 1987 and 1992 follow-up examination reports and “1987 dioxin” in the 1997 and 2002 follow-up examination reports.

When 1987 dioxin levels were examined for Comparisons, the vast majority of levels (approximately 98%) were below 10 ppt (8). The median 1987 dioxin level for Ranch Hands, however, was 11 ppt, and there was a distinct difference among military occupation categories. The median dioxin level was 24 ppt for enlisted groundcrew, 16 ppt for enlisted flyers, and 7 ppt for officers. The patterns within military occupation appeared to agree with Ranch Hand crew chief interviews conducted before the results of the assay became available to AFHS participants (9).

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the “earlier” tour of duty throughout this report) and whose difference was at most 18.6 years (referred to as the “later” tour of duty throughout this report).

Analyses performed using earlier and later tours of duty allowed investigation of the 1987 dioxin relation with health in relation to time. For example, if there were no relation between a measure of health and dioxin in the first few years after exposure, and a strong relation many years after exposure, there may be no association for Ranch Hands with later tours and an association for Ranch Hands with earlier tours. It is important to note that an effect of this kind could be due to the passage of time or to a higher initial dioxin level received by Ranch Hands with earlier tours, or both.

2.5 THE ORIGINAL AFHS EXPOSURE INDEX VERSUS SERUM DIOXIN MEASUREMENTS

In the first three AFHS reports, summarizing results of physical examinations conducted in 1982, 1985, and 1987, the potential relation between health endpoints and herbicide exposure in Ranch Hand veterans was assessed using the original AFHS exposure index. Six different herbicides were used in the RVN by Operation Ranch Hand to defoliate by aerial spraying from C-123 aircraft. From 1962 through 1965, small quantities of Agents Purple (2,4-D; 2,4,5-T), Blue (cacodylic acid), Pink (2,4,5-T), and Green (2,4,5-T) were sprayed. From 1965 through 1970, more than 11 million gallons of Agent Orange (2,4-D, 2,4,5-T) and smaller quantities of White (2,4-D, picloram) and Blue were sprayed; from 1970 through 1971 only Agents White and Blue were used for defoliation purposes (10). The exposure index was only an estimate of dioxin exposure because the actual concentration of dioxin in the herbicides varied with type and lot and because exposure varied with individual work habits and duties. The calculation of the index was necessary because direct measures of dioxin exposure were not available at that time.

The original AFHS exposure index was based on the untested assumption that the exposure of an individual decreased as the number of men available increased. The calculation was performed for each month of an individual's tour of duty, and the monthly results were summed to produce a single exposure index for each Ranch Hand veteran. Each veteran was then assigned to a low, medium, or high exposure category. These categories were of nearly equal size, and the cutpoints for these categories were different for the three military occupational categories (officer, enlisted flyer, or enlisted groundcrew).

Subsequent to 1987, all outcomes in this study were assessed with group contrasts and the dioxin body burden measured in serum. The 1987 results were analyzed twice, first using the original AFHS exposure index (11), and then using the dioxin body burden as the measure of exposure (6).

The Ranch Hand Advisory Committee and the AFHS investigators believed the serum dioxin level was the most appropriate measure of exposure in this study because of the following:

- It was a direct measurement of the contaminant.
- It has been accurately measured (12).
- It correlated with reported skin exposure to herbicides among enlisted Ranch Hand veterans (9).
- Its elimination in Ranch Hand veterans followed a plausible pharmacokinetic pattern (7).
- It has been found to be plausibly associated with health conditions in this study and in other studies (13).

Both measures, the original AFHS exposure index and the serum dioxin measurement, have limitations. The exposure index was approximate in that the number of gallons sprayed used the totals across all bases rather than at a specific base. In addition, the assumption that exposure decreased as the number of men available increased may not have been reasonable. Interviews with Ranch Hand groundcrew in 1989 revealed that as the workload increased, more men were added to the job, resulting in more men becoming exposed rather than each man becoming less exposed. Finally, the spectrum of behaviors, skills, duties, weather-related work stoppages, work surges due to war conditions, and other factors (some known, some unknown) were not included in the calculation. For example, some Ranch Hand groundcrew had direct contact with bulk quantities of herbicide by filling the tanks and servicing the equipment, while others drove trucks or forklifts. The index did not distinguish between these two kinds of exposure patterns. In addition, some Ranch Hands were assigned to administrative duties, which were indicated in their military records. The original AFHS exposure index was defined as zero for those assigned to administrative duties.

The serum dioxin measurement is also limited as a measure of exposure. Although the half-life of dioxin is long (7.6 years), pharmacokinetic studies of Ranch Hand veterans suggested that the half-life varies with body fat (7). Thus, some veterans may eliminate dioxin quickly and others more slowly. Variation of the dioxin half-life with body fat contributed to variation in the extrapolated initial dose at the time of exposure. In addition, more than 45 percent of Ranch Hand veterans had background levels, precluding extrapolation. Some of those with background levels may have had elevated levels while in the RVN, while others may not have been occupationally exposed at all. The exposure status of Ranch Hands with background levels cannot be resolved with available data. Furthermore, no validated model exists to assess the adequacy of the estimated initial dose as an estimate of actual exposure among those with dioxin levels above background in 1987, 1992, 1997, or 2002. Use of serum dioxin measurements as a measure of exposure in the RVN is further confounded by the other possible sources of dioxin exposure. These sources include industrial exposure and environmental factors, such as burning of plastics and fish consumption.

Throughout the 1987, 1992, 1997, and 2002 follow-up examination reports, dioxin levels were used as measures of both exposure to dioxin itself and exposure to dioxin-contaminated herbicides, including Agent Orange. Direct contrasts of Ranch Hand and Comparison veterans (group analyses) addressed the hypothesis of health effects attributable to any herbicide exposure experienced by Ranch Hand veterans during Operation Ranch Hand. Models involving dioxin measurements addressed the hypothesis that health effects change with the amount of exposure. Dioxin measurements were used as a measure of exposure to dioxin-contaminated herbicides because it was expected that as exposure to such herbicides increased, dioxin levels should increase. Therefore, the dioxin measurement served as a direct biomarker of exposure to dioxin-contaminated herbicides. No other direct measure or estimate of herbicide exposure was available with which to address hypothetical dose-response relations with health. Some indirect measures, such as self-report of skin contact among enlisted groundcrew, or simply being a Ranch Hand enlisted groundcrew member, are valuable alternatives because dioxin measures suggest that enlisted groundcrew experienced the heaviest exposures. Reported skin exposure was not addressed, but enlisted groundcrew status was addressed in contrasts of Ranch Hands and Comparisons. The use of dioxin as a measure of exposure to dioxin-contaminated herbicides was consistent with the goal of the study, which was to determine whether adverse health effects exist and can be attributed to occupational exposure to Agent Orange (14).

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3 INTERPRETIVE CONSIDERATIONS

3.1 INTRODUCTION

In interpreting results from any epidemiological study, no single result should be evaluated in isolation or out of context. Rather, interpretations should be addressed in the context of the overall study design, the data collection procedures, the data analysis methods, dose-response effects, strength of association, temporal relation, biological plausibility, and internal and external consistency. This especially applies to the Air Force Health Study (AFHS). This effort was a large-scale prospective observational study in which thousands of measurements and diagnoses were compiled on each participant. Those measurements and diagnoses were subjected to extensive statistical analyses, testing thousands of individual hypotheses. Each positive result should be scrutinized relative to findings in other studies, and relative to the statistical methods used and the medical and biological plausibility of the results. Conversely, the lack of a positive result only denotes that the hypothesis of no association was not rejected. This has a very different conclusion than the possibly incorrect assertion that there is no effect. In addition, no epidemiological study can establish that there is no effect; i.e., that dioxin is safe (1). Critical considerations in the evaluation of results from this study are reviewed in this chapter.

3.2 STUDY DESIGN AND MODELING CONSIDERATIONS

Biased results will be produced if the assumptions underlying any of the statistical models are violated. As in any epidemiological study, the group contrast (Ranch Hands versus Comparisons) is susceptible to bias toward the null hypothesis of no exposure effect because of possible exposure misclassification. It may not be true that all Ranch Hands and no Comparisons were occupationally exposed. Recent dioxin data indicate that 45 percent of the Ranch Hands have only background serum dioxin levels. Either these Ranch Hands were never exposed or their initially elevated serum dioxin levels may have decreased to background levels during the time period between exposure and serum dioxin measurement. The AFHS has no additional data with which to determine whether Ranch Hands who have background dioxin levels had elevated levels in the past because there was no method of measuring dioxin in blood prior to 1987 and because no blood was collected and saved prior to 1982.

Analyses of the association between health endpoints and extrapolated initial dioxin levels also are vulnerable to bias because they directly depend on two unvalidated assumptions: (a) that dioxin elimination is by first-order pharmacokinetics, and (b) that all Ranch Hands have the same dioxin half-life. If dioxin elimination is first-order, but some Ranch Hands have a shorter half-life than others do, then there would have been misclassification of initial dioxin levels.

The half-life of dioxin was found to change with body mass index in 213 Ranch Hand veterans with up to four dioxin measurements, derived from serum drawn in 1982, 1987, 1992, and 1997 (2). The half-life increased with higher levels of obesity. A constant half-life was used in each report and was an estimate derived without adjustment for body mass index (2). As a partial solution to the observed relation between half-life and obesity, analyses using categorized dioxin or initial dioxin were adjusted for body mass index at the time of the blood measurement of dioxin. A study of dioxin elimination in 20 men exposed during the accident in Seveso, Italy, has validated the first-order model (3), which was the basis for the half-life estimate used in this report. Validated models of dioxin elimination adjusted for body mass index or changes in body mass index, however, have not yet been derived.

To account for the possible misclassification of exposure between groups, the statistical model using categorized dioxin classifies Ranch Hands into three levels of exposure: background levels of lipid-adjusted dioxin and low and high levels of estimated initial dioxin. Each Ranch Hand dioxin category was contrasted with all Comparisons. Although this model was less dependent on the accuracy of the initial dioxin estimation procedure than the model using continuous initial dioxin estimates, the classification of the Ranch Hands is subject to bias if the half-life and first-order dioxin elimination assumptions are not true. In addition, the Ranch Hands with background levels of lipid-adjusted serum dioxin may contain both unexposed Ranch Hands and exposed Ranch Hands whose serum dioxin levels have decreased to background levels. This will result in a bias toward the null hypothesis of no dioxin effect on the health endpoint.

The model that analyzes the association between a 1987 dioxin measurement and health endpoints may be less subject to bias than other models that use dioxin as an exposure measure; however, recent dioxin levels may not be a good measure of exposure if serum dioxin elimination rates differed among individuals. Serum dioxin levels were extrapolated from 1992 measurements to 1987 for Ranch Hand veterans without serum dioxin levels measured in 1987. Serum dioxin levels also were extrapolated from 1997 measurements to 1987 for Ranch Hand veterans without levels measured in 1987 or 1992. In addition, serum dioxin levels were extrapolated from 2002 measurements to 1987 for Ranch Hand veterans without levels measured in 1987, 1992, or 1997. These extrapolations were performed only if the most recent measurement was greater than 10 parts per trillion (ppt). Therefore, these 1987 dioxin measurements are subject to bias from a possible violation of the half-life and first-order elimination assumptions that may affect the initial dioxin estimates. It is recognized that the serum dioxin level may have been greater than 10 ppt in 1987, but measurements taken from 1992, 1997, or 2002 may have been at 10 ppt or less and may eliminate individuals whose levels were above 10 ppt during the prior years, resulting in misclassification.

3.3 INFORMATION BIAS

Information bias, represented by the over- or under-reporting of disease symptoms, was minimized by verifying all diseases and conditions with medical records. It is possible that conditions in Ranch Hands may be more verifiable because they may have been seen by physicians more often than Comparisons. This would be revealed by group differences in the quantity and content of medical records. Because there is no way to quantify these aspects, this potential source of bias remains unexplored. This bias, if it existed, would affect only the models contrasting Ranch Hands and Comparisons (group analyses and categorized dioxin analyses). Information bias due to errors in the data introduced through data entry or machine error was negligible. All laboratory results were subject to strict quality control procedures, historical data were verified completely by medical records review, and medical data were subjected to strict quality control standards.

3.4 CONSISTENCY OF RESULTS

All statistically significant findings in the baseline and follow-up reports were subjected to clinical review, ensuring internal consistency throughout the report. In addition, these findings were compared to published results from other studies to ensure external consistency.

3.5 STRENGTH OF ASSOCIATION

A strong adverse association between exposure and a disease condition, if it exists, would be revealed by an increased relative risk. Some authors have suggested that a statistically significant relative risk greater than 2.0 is cause for concern (4). Statistically significant relative risks less than 2.0 are generally considered to be less important than larger risks because relative risks less than 2.0 can arise more easily because of unrecognized bias or confounding. Relative risks greater than 5.0 are less subject to this concern. The numbers 2.0 and 5.0 are epidemiological guidelines regarding analyses of association between a dichotomous endpoint (disease, no disease) and exposure (yes, no). No such general guidelines have been formulated regarding the analysis of continuously distributed endpoints (such as cholesterol) versus continuously distributed exposure (such as extrapolated initial dioxin estimates or serum dioxin measurements).

Statistical power is also an issue in a study with a population this size. A study with a population of the approximately 2,000 veterans who completed physical examinations lacks power to determine increases in relative risks for rare events (such as soft tissue sarcoma) because such events are unlikely to occur in large numbers in a group this small. While certain occupational toxins have a clear diagnostic pathology (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) virtually nonexistent in the absence of the causative agent, other toxins merely increase the risk of nondiagnostic pathology. For example, the AFHS would likely not discern an increase in the relative risk for a rare tumor that does not have a clear diagnostic pathology. By assessing the pathology observed in association with other known environmental risk factors (e.g., tobacco use, alcohol use), it is sometimes possible to provide a limit in the magnitude of effect missed; however, this study has inherent bounds in detecting modest increases in relative risk for infrequent pathology.

3.6 RESULTS BASED ON INDIRECT MEASURES OF THE VIETNAM EXPERIENCE AND HERBICIDE EXPOSURE

Interpretations of cohort contrasts in this study have been limited because, by design, both cohorts comprised veterans of the Vietnam War. Thus, the study was not designed to assess directly the Southeast Asia (SEA) or Vietnam experience but rather the effect, if any, of occupational exposures to herbicides, with specific emphasis on Agent Orange, in Ranch Hand veterans relative to other Vietnam veterans who were not occupationally exposed. A "Vietnam" effect, if equally expressed by Ranch Hand and Comparison veterans, would not be detectable in this study.

The primary focus of this study was the potential effects of herbicide/dioxin exposure on health outcomes. The flexibility of the statistical methodology and the comprehensive nature of the data collected, however, permitted the analysis of other factors, as allowed for in the AFHS protocol (5). Because it was impossible to know exactly the kind and amount of herbicide or other chemical exposures experienced during the Vietnam War by AFHS veterans, indirect measures of the Vietnam experience and herbicide exposure based on general knowledge of the Vietnam War, as derived from published accounts, have been considered. Morbidity analyses of cancer incidence, in which the Ranch Hand and Comparison cohorts were stratified by time spent in the SEA region and the percentage of SEA service spent in Vietnam, have been performed. Analyses of cancer incidence using the national population as a reference, with and without restriction to dates of tour, also have been conducted.

Stratifications of AFHS participants that have been analyzed include (a) restriction of length of tour of duty to at most 2 years, and (b) restriction to Ranch Hand veterans with 100 percent of their SEA service spent in the Republic of Vietnam (RVN) and Comparison veterans with 0 percent of their SEA service spent in the RVN. These stratifications were attempts to maximize the Agent Orange exposure

opportunity among Ranch Hand veterans and minimize it among Comparison veterans. Categorizing veterans by the amount of time spent in SEA approximated categorization by the percentage of SEA service spent in Vietnam. Stratification by the percentage of SEA service in Vietnam gave a clearer dichotomy on the Vietnam experience.

Results of cancer incidence analyses using these restrictions have been described in a 2004 journal article by Akhtar et al. (6). Analyses found that the incidence of melanoma and prostate cancer was increased among white Ranch Hand veterans after restriction to participants whose tour of duty occurred between 1966 and 1970, the period of heaviest Agent Orange spraying. Among Ranch Hands who spent at most 2 years in SEA, the risk of cancer at any site was increased in the low and high dioxin categories relative to Comparisons who spent at most 2 years in SEA. Among Ranch Hands who spent 100 percent of their SEA tour(s) of duty in Vietnam, the risk of cancer at any site was increased in the low and high dioxin categories relative to Comparisons who spent 0 percent of their SEA tour(s) of duty in Vietnam.

Analyses of this type demonstrate that effects not observed in the entire population may be seen in subgroups of AFHS veterans. In addition, analyses based on stratification by operational factors, rather than nonmedical risk factors, may yield results in certain subgroups. Stratification, however, can limit the ability to detect a difference because of the inherent reduction in sample size. The series of reports for the AFHS have focused on analyses based on standard epidemiological models that use known medical and demographic risk factors, but additional analysis on subpopulations with alternative risk factors may yield different results.

3.7 BIOLOGICAL PLAUSIBILITY

The assessment of biological plausibility requires consideration of a biological mechanism relating the exposure and effect of interest. While a lack of biological plausibility or even a contradiction of biological knowledge can lead to the dismissal of a significant result, the failure to perceive a mechanism may reflect only ignorance of the state of nature. On the other hand, it is easy to hypothesize biological mechanisms that relate almost any exposure to almost any disease. Thus, while important, the biological explanation of results must be interpreted with caution. In the AFHS, statistically significant results were subjected to medical review and comparison with previously published results to identify consistent and biologically plausible results.

3.8 INTERPRETATION OF NONSIGNIFICANT RESULTS

In this study, a lack of significant results relating dioxin to a particular disease only means that the study was unable to detect a relation between dioxin and health. This does not imply that a relation may not exist, but that if it does exist, it was not detected. A lack of significant results does not mean that dioxin is safe or that there is no relation between dioxin and health. The AFHS was not designed to establish safety; rather, this study was designed to determine whether a hazard existed for the exposed personnel. Determination of safety would require a study at least 10 times as large, as determined in a 1985 study presenting minimal sample size criteria for proof of safety and hazard in studies of environmental and occupational exposures (1).

3.9 EXTRAPOLATION TO ARMED FORCES GROUND TROOPS

Extrapolation of the serum dioxin results to the general population of ground troops who served in Vietnam is problematic because Ranch Hand and ground troop exposure situations were very different

from one another. Based on serum dioxin testing results obtained by the Centers for Disease Control and Prevention (7) and others (8), nearly all ground troops tested had 1987 levels of dioxin similar to background levels. Even combat troops who served in herbicide-sprayed areas of Vietnam had 1987 dioxin levels similar to those in men who never left the United States (with mean dioxin levels of 4.2 ppt and 4.1 ppt, respectively). There is little scientific basis for an extrapolation of these results to the larger population of Vietnam veterans. The possibility that a limited number of veterans could have been exposed to levels of dioxin comparable to the Ranch Hand veterans cannot be excluded, but because blood or adipose tissue were not collected immediately after their return from Vietnam, the actual exposures of these veterans cannot be known. Others may have received long-term low-dose exposure. These possibilities and a multitude of factors, including differential elimination and exposures to other persistent organic pollutants, suggest that existing data do not provide an adequate basis for extrapolation.

3.10 CONSIDERATIONS FOR SUMMARIZING RESULTS

A study of this scope with a multitude of endpoints demands, and at the same time defies, meaningful summary tabulation. Such summaries can be misleading because they ignore correlations between the endpoints, correlations between examination results, and the nonquantifiable medical importance of each endpoint. In fact, some endpoints were indices developed from combining multiple endpoints. Other endpoints, such as psychological scales, may be highly associated with other similar endpoints. In addition, such tabulations combine endpoints that are not medically or biologically comparable. For example, diminished sense of smell may be of less medical importance than the presence of a malignant neoplasm. Summaries can be misleading and must be interpreted carefully—an elementary tally of significant, or nonsignificant, results is not appropriate.

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4 ILLNESSES PRESUMPTIVELY RECOGNIZED AS AGENT ORANGE-CONNECTED

4.1 INTRODUCTION

Any veteran who served in Vietnam between January 9, 1962, and May 7, 1975, and has one or more of the following conditions is presumed by the Department of Veterans Affairs to have been exposed to Agent Orange, and, therefore, presumptively recognized that his condition is service-connected (1, 2):

- Acute and subacute transient peripheral neuropathy (must appear within 1 year of exposure and resolve within 2 years of date of onset)
- Chloracne (must occur within 1 year of exposure)
- Chronic lymphocytic leukemia
- Hodgkin's disease
- Multiple myeloma
- Non-Hodgkin's lymphoma
- Porphyria cutanea tarda (PCT) (must occur within 1 year of exposure)
- Prostate cancer
- Respiratory cancers, including cancers of the lung, larynx, trachea, and bronchus
- Soft tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma)
- Spina bifida (in children of Vietnam veterans born after the veteran's tour in Vietnam) (except spina bifida occulta)
- Type 2 diabetes.

Congress directed the Secretary of Veterans Affairs in Public Law 102-4, signed on February 6, 1991, to request the National Academy of Sciences to conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used during the Vietnam War. In 1994, the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides published its first report (4). This report classified evidence of an association between a health problem and exposure to herbicides as "sufficient," "limited/suggestive," or "inadequate/insufficient." The evidence regarding association was drawn from occupational, environmental, and veterans studies in which individuals were exposed to the herbicides used in Vietnam, to their components, or to their contaminants. Since this report, the IOM has published five biennial updates—1996, 1998, 2000, 2002, and 2004—incorporating results from additional studies (5-9). The work of this committee has provided the Department of Veterans Affairs

with the necessary information to create the list of compensable conditions described above. The recommendations from this committee are included in further discussion of these conditions in this chapter.

In the subsequent descriptions of the compensable conditions given above, summaries of Ranch Hands in each of the dioxin categories (background, low, or high) are often provided. Ranch Hands in the background dioxin category had a measured dioxin level of 10 parts per trillion (ppt) or less. Ranch Hands in the low dioxin category had a measured dioxin level of greater than 10 ppt and an estimated initial dioxin level of 118 ppt or less. Ranch Hands in the high dioxin category had a measured dioxin level of greater than 10 ppt and an estimated initial dioxin level of greater than 118 ppt.

A dioxin measurement was available for 1,027 of the 1,197 Ranch Hands for whom medical records were available. Of these 1,027 Ranch Hands, 452 were in the background dioxin category, 287 were in the low dioxin category, and 288 were in the high dioxin category. Of the 170 Ranch Hands for whom a dioxin level was not available, 148 did not participate in the Air Force Health Study (AFHS) after the 1985 follow-up examination, and the serum dioxin measurement was not available until the 1987 follow-up examination.

A dioxin measurement was available for 1,524 of the 1,855 Comparisons for whom medical records were available. Of these 1,524 Comparisons, 1,489 Comparisons had a measured dioxin level of 10 ppt or less and 35 Comparisons had a measured dioxin level of more than 10 ppt. Of the 331 Comparisons for whom a dioxin level was not available, 305 did not participate in the AFHS after the 1985 follow-up examination, and the serum dioxin measurement was not available until the 1987 follow-up examination.

Findings from the AFHS for these conditions are described in the remainder of this chapter. Descriptions of each of these conditions have been taken from the April 2005 Veterans Affairs' *Agent Orange Review* (3). The term "compound of interest" in the discussions includes 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, or dioxin), cacodylic acid, and picloram.

4.2 ACUTE AND SUBACUTE TRANSIENT PERIPHERAL NEUROPATHY

Peripheral neuropathy is a nervous system condition that causes numbness, tingling, and muscle weakness. This condition affects only the peripheral nervous system, that is, only the nervous system outside the brain and spinal cord. Only the transient (short-term) acute and subacute forms of this condition, not the chronic persistent forms, have been associated with herbicide exposure.

No Ranch Hands or Comparisons were observed with acute or subacute transient peripheral neuropathy in the AFHS.

In the 1996 *Veterans and Agent Orange* update (5), the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides concluded that there is "limited/suggestive" evidence of an association between exposure to certain herbicides used in Vietnam and the development of early onset (previously termed "acute and "subacute") transient peripheral neuropathy. This conclusion remained unaltered in the 2004 *Veterans and Agent Orange* update (9). In this report, however, the committee added that there was inadequate or insufficient "evidence to determine an association between exposure to compounds of interest and delayed or persistent peripheral neuropathy."

4.3 CHLORACNE

Chloracne is a skin condition that looks like common forms of acne seen in teenagers. The first sign of chloracne may be excessive oiliness of the skin. This is accompanied or followed by numerous blackheads. In mild cases, the blackheads may be limited to the areas around the eyes extending to the temples. In more severe cases, blackheads may appear in many places, especially over the cheekbone and other facial areas, behind the ears, and along the arms. If chloracne appears, however, it is usually after a short interval of exposure to dioxin, without a long latency period, and usually persists for a maximum of 2 to 3 years.

No Ranch Hands or Comparisons were observed with chloracne in the AFHS.

In the first *Veterans and Agent Orange* report in 1994 published by the IOM, the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides concluded that there is sufficient evidence of an association between exposure to dioxin and chloracne (4). This conclusion remained unaltered in the 2002 *Veterans and Agent Orange* update (8); however, the committee added a notation that chloracne would appear shortly after dioxin exposure and not after a long latency (8). The 2004 *Veterans and Agent Orange* update concurred with previous reports (9).

4.4 CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia is a disease that progresses slowly with increasing production of excessive numbers of white blood cells. In the 2004 *Veterans and Agent Orange* update, the epidemiologic evidence was considered by the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides to be “sufficient” concerning chronic lymphocytic leukemia, and “exposure to at least one compound of interest (9).”

Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, five Ranch Hands and six Comparisons had chronic lymphocytic leukemia. Three of the Ranch Hands with chronic lymphocytic leukemia were in the background dioxin category, one of the Ranch Hands was in the low dioxin category, and one Ranch Hand did not have a dioxin measurement. The six Comparisons with chronic lymphocytic leukemia had a measured dioxin level less than 10 ppt.

In 2004, the AFHS staff and colleagues published one journal article related to cancers of the lymphopoietic system, where lymphomas, multiple myeloma, and leukemia were combined because of a sparse number of occurrences (10). No adverse effects to Ranch Hands were noted in this analysis.

4.5 HODGKIN'S DISEASE

Hodgkin's disease is a malignant lymphoma characterized by progressive enlargement of the lymph nodes, liver, and spleen, and by progressive anemia. The IOM, as reported in the first *Veterans and Agent Orange* book in 1994 on the health effects of herbicides used in Vietnam (4), concluded that there is “sufficient” evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of Hodgkin's disease (4). The 2004 *Veterans and Agent Orange* update stated that an association existed between exposure to at least one of the compounds of interest and Hodgkin's disease (9).

Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, one Ranch Hand and three Comparisons had Hodgkin's disease. The Ranch Hand with Hodgkin's disease was in the

background dioxin category. The three Comparisons with Hodgkin's disease had a measured dioxin level less than 10 ppt.

4.6 MULTIPLE MYELOMA

Multiple myeloma is a cancer of specific bone marrow cells that is characterized by bone marrow tumors in various bones of the body. The evidence for an association, although not a causal relation, between dioxin exposure and the occurrence of multiple myeloma was considered "limited/suggestive" by the IOM Committee in the first *Veterans and Agent Orange* report and all updates (4-9).

Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, four Ranch Hands and one Comparison had multiple myeloma. One of the Ranch Hands with multiple myeloma was in the background dioxin category and three were in the low dioxin category. The one Comparison with multiple myeloma had a measured dioxin level less than 10 ppt.

4.7 NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphoma is a group of malignant tumors that affect the lymph glands and other lymphatic tissue. These tumors are relatively rare compared to other types of cancer, and although survival rates have improved during the past 2 decades, these diseases tend to be fatal.

Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, two Ranch Hands and seven Comparisons had non-Hodgkin's lymphoma. One of the Ranch Hands with non-Hodgkin's lymphoma was in the background dioxin category and one was in the high dioxin category. Six of the seven Comparisons with non-Hodgkin's lymphoma had a measured dioxin level; one of these six Comparisons had a measured dioxin level greater than 10 ppt.

The IOM, as reported first in their 1994 book on the health effects of herbicides used in Vietnam (4), concluded that there is "sufficient" evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of non-Hodgkin's lymphoma (4-9). In the 2004 *Veterans and Agent Orange* update, the committee concluded there was sufficient evidence to conclude that an association existed between exposure to at least one compound of interest and non-Hodgkin's lymphoma (9).

4.8 PORPHYRIA CUTANEA TARDA (PCT)

PCT is a disorder characterized by liver dysfunction and by thinning and blistering of the skin in sun-exposed areas. The IOM, as reported first in their 1994 book on the health effects of herbicides used in Vietnam (4), concluded that there is "sufficient" evidence to establish an association, although not a causal relation between herbicides or dioxin and PCT. In the 1996 report, the association with PCT was downgraded from "sufficient" to "suggestive" evidence, based on studies completed since the first IOM report (5). The 2004 *Veterans and Agent Orange* update continued to support a finding of "limited/suggestive" evidence between herbicides and PCT (9).

No Ranch Hands or Comparisons were observed with PCT in the AFHS.

4.9 PROSTATE CANCER

The IOM Committee concluded that there is “limited/suggestive” evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of prostate cancer in the first *Veterans and Agent Orange* report and all updates (4-9).

Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, 63 Ranch Hands and 93 Comparisons had prostate cancer. Of the 63 Ranch Hands with prostate cancer, 25 Ranch Hands were in the background dioxin category, 27 were in the low dioxin category, 10 were in the high dioxin category, and 1 Ranch Hand did not have a dioxin measurement. Of the 93 Comparisons, 90 had a measured dioxin level, and 1 of these 90 Comparisons had a measured dioxin level greater than 10 ppt.

The AFHS staff and colleagues published three journal articles related to cancer, which include prostate cancer as one of the categories analyzed (10-12). A further discussion of these articles is found in Chapter 14 – Neoplasia Assessment.

4.10 RESPIRATORY CANCERS, INCLUDING CANCERS OF THE LUNG, LARYNX, TRACHEA, AND BRONCHUS

The evidence for an association, although not a causal relation, between dioxin exposure and the occurrence of respiratory cancers was considered “limited/suggestive” by the IOM Committee (4-9).

Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, 44 Ranch Hands and 59 Comparisons had respiratory cancer. Of the 44 Ranch Hands with respiratory cancer, 14 Ranch Hands were in the background dioxin category, 14 were in the low dioxin category, 2 were in the high dioxin category, and 14 Ranch Hands did not have a dioxin measurement. Of the 59 Comparisons, 42 had a measured dioxin level, and 1 of these 42 Comparisons had a measured dioxin level greater than 10 ppt.

4.11 SOFT TISSUE SARCOMA (OTHER THAN OSTEOSARCOMA, CHONDROSARCOMA, KAPOSI'S SARCOMA, OR MESOTHELIOMA)

Soft tissue sarcoma is a group of different types of malignant tumors that arise from body tissues, such as muscle, fat, blood and lymph vessels, and connective tissues (not in hard tissue such as bone and cartilage). These cancers are in the soft tissue that occurs with and between organs.

Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, one Ranch Hand and five Comparisons had a soft tissue sarcoma. The Ranch Hand with a soft tissue sarcoma was in the background dioxin category. All five Comparisons with a soft tissue sarcoma had a measured dioxin level, and one of these five Comparisons had a measured dioxin level greater than 10 ppt.

The IOM Committee, as reported first in their 1994 book on the health effects of herbicides used in Vietnam (4), concluded that there is “sufficient” evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of soft tissue sarcoma (4). This conclusion has remained unchanged in all *Veterans and Agent Orange* updates (5-9).

4.12 SPINA BIFIDA (IN CHILDREN OF VIETNAM VETERANS) (EXCEPT SPINA BIFIDA OCCULTA)

Spina bifida is a neural tube birth defect that results from the failure of the bony portion of the spine to close properly in the developing fetus during early pregnancy. Among 792 live-born infants to Ranch Hand fathers and 981 live-born infants to Comparison fathers, four children from Ranch Hand fathers and zero children from Comparison fathers had spina bifida or anencephaly, which were both neural tube defects (13). Two of the Ranch Hands were in the low dioxin category and two Ranch Hands were in the high dioxin category (14). This result, along with two other epidemiological studies, led the IOM to conclude that there was limited/suggestive evidence of an association between exposure to herbicides and spina bifida in the offspring of exposed individuals, as reported in the 1996 *Veterans and Agent Orange* update (5). This conclusion remained the same in subsequent *Veterans and Agent Orange* updates in 1998, 2000, 2002, and 2004 (6-9).

4.13 TYPE 2 DIABETES

Type 2 diabetes, or diabetes mellitus, is characterized by high blood sugar levels resulting from the body's inability to respond properly to the hormone insulin.

Among 1,197 Ranch Hands and 1,855 Comparisons for whom medical records were available, 188 Ranch Hands and 309 Comparisons had type 2 diabetes. Of the 188 Ranch Hands with type 2 diabetes, 49 Ranch Hands were in the background dioxin category, 60 were in the low dioxin category, 69 were in the high dioxin category, and 10 Ranch Hands did not have a dioxin measurement. Of the 309 Comparisons with type 2 diabetes, 293 had a measured dioxin level, and 9 of these 293 Comparisons had a measured dioxin level greater than 10 ppt.

The AFHS staff and colleagues published nine journal articles related to diabetes and glucose control (15-23). A further discussion of these articles is found in Chapter 9 – Endocrinology Assessment.

Epidemiologic studies suggested that any increased risk of Type 2 diabetes from herbicide or dioxin exposure is small when compared to the known predictors—family history, obesity, physical inactivity—for diabetes. Based on its comprehensive review of the literature, the IOM found limited or suggestive evidence of an association between exposure to herbicides, including 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant dioxin, and Type 2 diabetes (7, 24). This conclusion remained unchanged in the 2002 and 2004 *Veterans and Agent Orange* updates (8, 9).

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5 REPRODUCTIVE OUTCOMES

5.1 INTRODUCTION

The possibility of an increased risk in birth defects in children of Vietnam veterans has caused veterans, the general public, and federal and state legislatures concern about possible dioxin exposure received by veterans during the Vietnam War. At the Air Force Health Study (AFHS) baseline examination in 1982, reproductive outcome information was collected and the results of the analysis of these data were included as part of the report for this examination. The data were based on birth defects reported by the mothers of the children and supplemented by information from the father as needed. At the time of analysis in 1984, this reported information had not yet been verified. Records necessary for verification were located and obtained, beginning in 1985. During the same period, analytical chemists at the Centers for Disease Control and Prevention (CDC) developed an assay for dioxin in serum and demonstrated its suitability as a substitute for the assay of dioxin in adipose tissue obtained by biopsy. Subsequent analysis of reproductive outcomes related birth defects to paternal serum dioxin levels (1-3).

A section of the 1982 baseline examination report described reproductive outcomes based on spouse-reported information. A supplemental technical report (4) was written based on the 1982 baseline report (5), but the supplemental report was updated and based on verified outcomes rather than self-reported information. A report in 1992 (6) presented the results of reanalysis based on verified information in conjunction with paternal serum dioxin levels. A series of journal articles were written based on the 1992 report. The findings described in these reports and articles are summarized below.

5.2 1982 BASELINE EXAMINATION

Analysis performed for the 1982 baseline examination revealed no difference between Ranch Hands and Comparisons for infertility, sperm count, or sperm abnormalities, based on semen collected from the participants at this examination (5). The conception outcomes of miscarriage, stillbirth, induced abortion, and live birth also were not different between spouses or partners of Ranch Hands and Comparisons. An association between increasing herbicide exposure and miscarriage was identified in Ranch Hand officers, but this effect was not seen for other military occupations (i.e., enlisted flyers, enlisted groundcrew).

An increase in the post-Southeast Asia (SEA) live birth outcomes of physically handicapped, all birth defects, and neonatal death for children of Ranch Hands was found based on data provided by participants and spouses in separate questionnaires administered at the baseline examination. An association between increasing herbicide exposure and birth defects was observed in Ranch Hand officers and enlisted flyers.

These birth defect findings at the baseline examination required further evaluation of the data. The analyses for the baseline report relied heavily on unverified spouse reports. The techniques used for collecting data stressed biologically born children, but the collection inadvertently resulted in information on multiple adopted and stepchildren in addition to the biologically born children. Subsequent analysis was conducted using birth certificates and medical records to verify fertility and reproductive outcomes.

5.2.1 Analysis of Live Birth Outcomes - Update

Since the release of the baseline morbidity report in February 1984, birth defects and neonatal deaths reported by study participants and their spouses during the administration of the baseline questionnaire were verified by a review of records. This verification was accomplished by the review of birth and other medical records, birth certificates, and death certificates. An update of this 1984 report was published as an Air Force technical report (4).

The percentage of reported neonatal deaths that was verified was not different among Ranch Hands, Original Comparisons, and all Comparisons; therefore, bias in the reporting of responses between groups did not appear to be present.

The results that were found based on verified data were comparable to the results based on self-reported data. There was a change in the relation between birth defects and group (i.e., Ranch Hand, Comparison), depending on whether the conception was prior to or after the father's service in SEA. More verified birth defects for conceptions prior to the father's service in SEA were found for Comparisons than for Ranch Hands, but more verified birth defects for conceptions after the father's service in SEA were found for Ranch Hands than for Comparisons. Reviewers from the Advisory Committee on Phenoxy Herbicides have questioned the relevance of these pre-SEA birth defect findings (7).

A change was also indicated in the relation between neonatal deaths and group, depending on whether the death was prior to or after the father's service in SEA. The percentage of neonatal deaths was similar in Ranch Hands and Comparisons for births prior to the father's service in SEA, but after the father's service in SEA, more neonatal deaths occurred among the children of Ranch Hand fathers than of Comparison fathers.

5.3 1992 REPRODUCTIVE OUTCOMES REPORT

The uncertainties surrounding unverified participant and spouse reports prompted the verification of reproductive outcomes. Participants and spouses separately reported fertility information at the 1982, 1985, and 1987 examinations. A review of birth certificates, newborn clinic records, health records, and death certificates was conducted. The health status of each child was verified through the age of 18. A total of 1,098 Ranch Hands and 1,549 Comparisons fathered 8,263 pregnancies and 6,792 live births. In addition, serum dioxin levels became available in 1986 (see Chapter 2) as an estimate of exposure for a subset of these veterans. A dioxin level had been determined by August 1991 for 791 Ranch Hands and 942 Comparisons; 5,489 pregnancies and 4,514 live births were fathered by these veterans. A report was released in August 1992 that described the results of the analysis of reproductive outcomes in conjunction with serum dioxin levels (6).

The analysis of birth defects in the AFHS baseline report found that the Ranch Hand rate of reported pre-SEA birth defects was less than the Comparison rate, and the Ranch Hand rate of reported post-SEA birth defects was greater than the Comparison rate. Reanalysis using verified data found similar results. Additional analyses, however, indicated no relation between paternal dioxin levels (initial, categorized, or 1987 dioxin) and the differential rates of pre-SEA and post-SEA birth defects.

The association between the father's dioxin level and sperm count and the percentage of abnormal sperm was assessed based on semen specimens collected during the 1982 baseline examination. No significant association was found between dioxin and sperm count or the percentage of abnormal sperm.

Miscarriages and adverse outcomes increased with increasing 1987 dioxin in conceptions fathered by Ranch Hands with late tours of duty, but decreased with increasing 1987 dioxin in conceptions fathered by Ranch Hands with earlier tours of duty. The highest number of post-SEA conceptions was found in Ranch Hands in the high dioxin category. The authors concluded that the results were mixed and biologically implausible and appear nonsupportive of a relation between dioxin and miscarriages.

The rate of abnormally low birth weights among children born after the Ranch Hand father's service in SEA was greater than the rate of abnormally low birth weights among children born prior to the Ranch Hand father's service in SEA. There was a decrease of a similar magnitude, however, in the rate of abnormally low birth weights children born after the Comparison father's service in SEA relative to children born prior to the Comparison father's service in SEA. The parallel increase in the rate of low birth weights in children of Ranch Hand fathers and the decrease in the rate of low birth weights in children of Comparison fathers relative to service in SEA lacked a biological explanation. When examining the birth weight itself, instead of the rate of abnormally low birth rates, the birth weight decreased with dioxin (initial, categorized, or 1987 dioxin) in some strata and increased in others. The mixed results of the birth weight analysis did not appear to suggest that birth weight was adversely associated with dioxin.

Few associations were found between dioxin and 13 individual categories of birth defects. Those associations that were noted, total congenital anomalies and musculoskeletal deformities, did not show increasing risks with increasing dioxin.

Major birth defects were defined, according to CDC definitions, as those defects that potentially can affect survival, result in marked physical or psychological handicaps, or interfere with a child's prospects for a productive and fulfilling life. No consistent patterns of association were found between the major birth defects and dioxin. In some analyses, the highest rates of major birth defects were found in children born to Ranch Hands with intermediate categorized dioxin levels, while the lowest rates were found in children born to Ranch Hands with the highest categorized dioxin levels. The results suggested no evidence that birth defect severity was adversely associated with dioxin.

Twelve specific birth defects and four developmental anomalies were investigated. There were only enough occurrences to permit statistical analysis on specific delays in development and hyperkinetic syndrome. Findings were few for both specific delays in development and hyperkinetic syndrome and often were in the direction opposite of what would have been expected with a dose-response relation.

Among 792 live-born infants to Ranch Hand fathers and 981 live-born infants to Comparison fathers, four children from Ranch Hand fathers and zero children from Comparison fathers had spina bifida or anencephaly, which are both neural tube defects. Two of the Ranch Hands were in the low dioxin category (extrapolated initial dose at or below 110 parts per trillion [ppt]) and two Ranch Hands were in the high dioxin category (extrapolated initial dose above 110 ppt) (1).

Of 1,772 births after the father's service in SEA, 57 had multiple birth defects that could not be attributed to recognized syndromes. The rate of multiple birth defects in children of Ranch Hands with the highest categorized dioxin levels was not elevated. The data did not support an association between dioxin and multiple birth defects.

Among children born after the Ranch Hand father's service in SEA, the rate of neonatal deaths (childhood death within 28 days of birth) was higher in children of Ranch Hands with the highest categorized dioxin levels than in children of Comparisons. Corresponding data, however, showed the same pattern among

children born before the Ranch Hand father's service in SEA. Therefore, the findings appeared to be due to chance rather than to paternal dioxin exposure.

In summary, the lack of an association between dioxin and total conceptions and between dioxin and sperm count or sperm abnormalities did not support the idea that dioxin was adversely related to the ability to father children. Dioxin also was unrelated to miscarriage, total adverse outcomes, birth weight, all 13 categories of birth defects, and neonatal death, and thus did not support the possibility of an adverse relation between dioxin and reproductive outcomes. The few positive associations that were found between dioxin and reproductive outcomes were generally weak, inconsistent, or biologically implausible.

5.3.1 AFHS Journal Articles Based on 1992 Reproductive Outcomes Report

The analyses for this report generated a series of journal articles on reproductive outcomes. The analysis reported in these journal articles were restricted to conceptions and children of veterans with dioxin results who were conceived during or after the father's service in SEA. A summary of these articles, which report similar findings to the 1992 reproductive outcomes report, is described below.

Few associations were found between dioxin and semen abnormalities, inability to conceive, prematurity, neonatal deaths, birth defects, birth defect severity, and developmental abnormalities (1). Associations were generally weak, inconsistent, or biologically implausible. There was no meaningful elevation in risk for spontaneous abortion or stillbirth.

There were some elevations in risk in some birth defect organ system categories, which, after review of the clinical descriptions, were not considered biologically meaningful. An increase in nervous system defects in children of Ranch Hands with increased paternal dioxin was observed, but it was based on sparse data. There was no indication of increased birth defect severity, delays in development, or hyperkinetic syndrome with paternal dioxin.

Verification of the existence, lineage, birth weight, gestation, and vital status of live births was attempted (2). No association was seen between paternal dioxin level and intrauterine growth retardation. The risk of infant death was increased among children of Ranch Hands whose fathers had the highest dioxin levels and among children whose fathers had background dioxin levels, but the pattern of results implied that the outcomes might not be related to paternal dioxin level.

Additional follow-up analyses on testosterone, follicle-stimulating hormone, luteinizing hormone, testicular abnormalities, and testicular volume were conducted on participants who attended the 1992 follow-up physical examination. No consistent or meaningful associations between serum dioxin levels and any of these outcome variables were observed. Analyses of testosterone in its continuous form indicated that there might have been a subclinical relation between dioxin and testosterone, but the association, if it existed, was too weak to be clinically meaningful (3).

5.4 CONCLUSION

The lack of an association between dioxin and total conceptions and between dioxin and any examined semen characteristics did not support the idea that dioxin was adversely related to the ability to father children. Dioxin also was unrelated to miscarriage, total adverse outcomes, birth weight, all 13 categories of birth defects, and neonatal death, and thus did not support the possibility of an adverse relation between dioxin and reproductive outcomes. The few positive associations that were found between dioxin and reproductive outcomes were generally weak, inconsistent, or biologically implausible.

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6 MORTALITY

6.1 INTRODUCTION

The Air Force Health Study (AFHS) protocol specified that the mortality of Ranch Hand and Comparison subjects be examined across the 20-year period of the AFHS. The United States Air Force (USAF) Military Personnel Center records, the Veterans Administration Death Beneficiary Identification and Record Location System, and the Internal Revenue Service database of active social security account numbers were used to determine the subjects' deaths. Death certificates were ordered from the vital statistics department of the appropriate state or foreign country. The underlying cause of death was classified according to National Center for Health Statistics decision tables. Veterans killed in action during the Vietnam War were excluded because the immediate effects of herbicide exposure were not thought to cause Ranch Hand combat deaths.

The AFHS protocol specified that up to 10 Comparisons were to be matched to each Ranch Hand according to date of birth, rank, race, and occupation, and that 5 Comparisons from each matched set were to be randomly chosen and used as the Comparison cohort for mortality studies. There were concerns that this randomly chosen Comparison cohort might not be representative of the mortality of all matched Comparisons. Data analyses performed prior to the 1989 Mortality Update (1) suggested that the mortality experience of the randomly chosen Comparison cohort was, purely by chance, not representative of the mortality experience of the entire matched Comparison cohort. After the concurrence of the Advisory Committee appointed by the Agent Orange Working Group, the Comparison cohort was expanded to include all matched Comparisons after the 1986 Mortality Update (2) and prior to the 1989 Mortality Update (1). No differences in the conclusions were seen in the 1989 Mortality Update (1), regardless of whether the randomly selected Comparisons or the entire Comparison cohort were used.

The published reports or articles displayed in the table below concern mortality in the AFHS population. A brief summary of these reports and articles is contained in the next section.

Report or Article	Verified Deaths through	Deaths (Population Size)	
		Ranch Hand	Comparison
Baseline Mortality Study Results (30 June 1983)	31 December 1982	50 (1,247)	250 (6,171)
Mortality Update – 1984 (10 December 1984)	31 December 1983	54 (1,256)	265 (6,171)
Mortality Update – 1985 (29 November 1985)	31 December 1984	55 (1,257)	285 (6,171)
Mortality Update – 1986 (26 December 1986)	31 December 1985	59 (1,257)	312 (6,171)
Mortality Update – 1989 (17 April 1989)	31 December 1987	74 (1,261)	376 (6,250)
Health Status of Air Force Veterans Occupationally Exposed to Herbicides in Vietnam 2. Mortality (in <i>The Journal of the American Medical Association</i>)	31 December 1987	74 (1,261)	1,039 (19,101)*
	31 December 1987	74 (1,261)	1,038 (19,101)*
	31 December 1987	74 (1,261)	1,038 (19,101)*
Mortality Update – 1991 (15 October 1991)	31 December 1989	91 (1,261)	1,241 (19,080)*
Mortality Update – 1993 (October 1993)	31 December 1991	106 (1,261)	1,439 (19,080)*
Mortality Update – 1994 (13 September 1994)	31 December 1992	111 (1,261)	1,545 (19,080)*
Mortality Update – 1996 (July 1996)	31 December 1993	118 (1,261)	1,672 (19,080)*

Report or Article	Verified Deaths through	Deaths (Population Size)	
		Ranch Hand	Comparison
Postservice Mortality of U.S. Air Force Veterans Occupationally Exposed to Herbicides in Vietnam: 15-Year Follow-up (25 March 1998) (in <i>American Journal of Epidemiology</i>)	31 December 1993	118 (1,261)	1,672 (19,080)*
Post-service mortality of Air Force veterans occupationally exposed to herbicides during the Vietnam War (May 2005) (in <i>Military Medicine</i>)	31 December 1999	186 (1,262)	2,330 (19,078)*

*: Comparison deaths based on all Comparisons; previous results were based on a randomly chosen cohort of five matched Comparisons.

Note: One additional death was verified between 1 April 1988 (cutoff date for verified deaths in *The Journal of American Medicine Association* article [3]) and 15 June 1988 (cutoff date for verified deaths in the 1989 Mortality Update [1]). This accounts for the difference in Comparison deaths between the two publications.

6.2 1983 BASELINE MORTALITY STUDY

As reported in the 1983 Baseline Mortality Study Results report (4), 50 Ranch Hand and 250 Comparisons had died as of 31 December 1982. Analyses showed that the mortality experience of the Ranch Hand group was nearly identical to that of the Comparison group. The authors cautioned, however, that this mortality report could in no way be regarded as conclusively negative because the study population may not have reached the latency period in which attributable fatal disease might have been expected and detected. The cohort of deaths at that time was small, and both the Ranch Hand and Comparison groups were young and relatively healthy.

6.3 1984 MORTALITY UPDATE

As of 31 December 1983, 54 Ranch Hands and 265 Comparisons had died. As described in the 1984 Mortality Update (5), no differences between Ranch Hand and Comparison mortality were found. Cause-specific analyses did not show any increased Ranch Hand mortality for accidents, suicide, homicide, malignancy, or circulatory system disease. No relation was found between mortality in Ranch Hands and the Air Force herbicide exposure index (described in Chapter 2). Continued mortality surveillance was recommended because the study groups were still relatively young and healthy.

6.4 1985 MORTALITY UPDATE

As of 31 December 1984, 55 Ranch Hands and 285 Comparisons had died. The analyses described in the 1985 Mortality Update (6) found no differences between Ranch Hand and Comparison mortality. Cause-specific analyses did not show any increased Ranch Hand mortality for accidents, suicide, homicide, malignancy, or circulatory system disease. No relation was found between mortality in Ranch Hands and the herbicide exposure index. An interaction involving age and military occupation, however, was discovered in these analyses. Older Ranch Hand officers (older than 35 years of age) experienced fewer deaths than older Comparison officers, but younger Ranch Hand officers (35 years of age or younger)

experienced more deaths than younger Comparison officers. Continued mortality surveillance was again recommended because the study groups were still relatively young and healthy.

6.5 1986 MORTALITY UPDATE

As of 31 December 1985, 59 Ranch Hands and 312 Comparisons had died, as reported in the 1986 Mortality Update (2). The conclusions and recommendations remained unchanged from the 1985 Mortality Update.

6.6 1989 MORTALITY UPDATE

The next AFHS Mortality Update was published in 1989 (1). A subsequent article in *The Journal of the American Medical Association* (3) also presented the results of this update. As of 31 December 1987, 74 Ranch Hands and 376 Comparisons had died, based on using the original Comparison cohort. For this update, the Comparison cohort was expanded to include the entire Comparison population who flew or serviced C-130 cargo aircraft in Southeast Asia (SEA) during the same calendar period that the Ranch Hand unit was active in Vietnam. This change in the Comparison cohort resulted in 74 Ranch Hands and 1,039 Comparison deaths as of 31 December 1987 (verified as of 15 June 1988).

As in previous updates, no differences between Ranch Hand and Comparison mortality were found in the 1989 Mortality Update (1). No difference between the observed and the expected number of deaths in Ranch Hands was seen when the cumulative mortality from all causes was examined. Cause-specific analyses did not show any increased overall Ranch Hand mortality for accidents, suicide, homicide, malignancy, or circulatory disease. Digestive system deaths were more frequent in Ranch Hands than expected. Five of the six digestive system deaths, however, were attributable to alcohol consumption; the finding was considered to be unrelated to herbicide exposure. No relation was found between mortality in Ranch Hands and the herbicide exposure index.

6.7 1991 MORTALITY UPDATE

As of 31 December 1989, 91 Ranch Hands and 1,241 Comparisons had died (using the entire Comparison population). The 1991 Mortality Update (7) was also the first report in which analysis of mortality in relation to serum dioxin levels was available (see Chapter 2). Prior to this report, the herbicide exposure index was used to assess dose-response trends within Ranch Hands.

Cause-specific analyses did not show any increased overall Ranch Hand mortality for accidents, suicide, malignancy, or circulatory disease. The increase of digestive system deaths in Ranch Hands continued; nine Ranch Hands died from digestive diseases. There was an excess of deaths from circulatory disease among Ranch Hand enlisted groundcrew personnel. The authors were concerned about this increase because Ranch Hand enlisted groundcrew had a higher median dioxin level than enlisted flyers or officers, and because dioxin levels were associated with diabetes and lipid abnormalities. Whereas there was no association between dioxin and cardiovascular disease in living Ranch Hands, it was considered possible that an increase in circulatory disease deaths could be dioxin-related through its association with diabetes and serum lipids.

6.8 1993 MORTALITY UPDATE

An evaluation of the cumulative Ranch Hand mortality from all causes through 31 December 1991 found no difference in the observed number of deaths from what was expected of a cohort of this size and age, as reported in the 1993 Mortality Update (8). As of this date, 106 Ranch Hands and 1,439 Comparisons had died. There was an increasing trend in death from all causes in Ranch Hand enlisted flyers during the 1989 to 1991 period. Of the seven Ranch Hand enlisted flyers who died during that period, five were due to a malignant neoplasm. This trend was not seen in Ranch Hand enlisted groundcrew, who were more heavily exposed to dioxin on average. The trend in enlisted flyers was a source of concern, but if these deaths were caused by exposure, a corresponding trend in enlisted groundcrew would have been expected.

Cause-specific analyses did not show any increased overall Ranch Hand mortality for accidents, suicide, homicide, deaths due to infectious or parasitic diseases, deaths due to a malignant neoplasm, deaths due to endocrine disease, or deaths due to circulatory disease. The increase in digestive system deaths in Ranch Hands continued, as did the increase in deaths from circulatory disease among Ranch Hand enlisted groundcrew personnel.

For 872 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no difference in the mean 1987 dioxin levels between 856 Ranch Hands who were still alive and the 16 Ranch Hands who were deceased as of 31 December 1991. There also was no relation between survival time and dioxin levels.

6.9 1994 MORTALITY UPDATE

As reported in the 1994 Mortality Update (9), no difference between the observed and the expected number of deaths in Ranch Hands was seen when the cumulative mortality from all causes through 31 December 1992 was examined. As of this date, 111 Ranch Hands and 1,545 Comparisons had died. Cause-specific analyses found no increase in overall Ranch Hand mortality from accidental deaths, suicides, homicides, deaths due to infectious and parasitic diseases, deaths due to malignant neoplasms, deaths due to endocrine disease, or deaths due to circulatory diseases. As with previous updates, the increase in digestive system deaths in Ranch Hands and deaths from circulatory disease among Ranch Hand enlisted groundcrew personnel was observed. A new finding on deaths due to ill-defined or unknown causes, however, was seen for the first time in this update. The number of deaths due to ill-defined or unknown causes increased among Ranch Hand enlisted flyers.

For 988 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no difference in the mean 1987 dioxin levels between 968 Ranch Hands who were still alive and the 20 Ranch Hands who were deceased as of 31 December 1992. There also was no relation between survival time and 1987 dioxin levels.

6.10 1996 MORTALITY UPDATE

No difference between the observed and the expected number of deaths in Ranch Hands was seen when the cumulative mortality from all causes through 31 December 1993 was examined. As reported in the 1996 Mortality Update (10), 118 Ranch Hands and 1,672 Comparisons had died. Cause-specific analyses found no increase in overall Ranch Hand mortality from accidental deaths, suicides, homicides, deaths due to infectious and parasitic diseases, deaths due to malignant neoplasms, deaths due to endocrine disease, deaths due to respiratory disease, deaths due to circulatory disease, or deaths due to ill-defined or unknown causes. An increase in deaths due to digestive disease was no longer seen, and an increase in

deaths in Ranch Hand enlisted flyers was no longer present. There were 30 deaths due to malignant neoplasms, but they did not appear to aggregate in an unusual pattern relative to what would have been expected. The increase in deaths from circulatory disease among Ranch Hand enlisted groundcrew that was reported since the 1991 Mortality Update (7) was still present, although no new circulatory disease deaths in this cohort were reported since the 1994 Mortality Update (9). Further analysis of circulatory disease deaths in enlisted groundcrew revealed that more than 65 percent of these deaths were due to atherosclerotic heart disease.

For 991 Ranch Hands who had a dioxin result, an analysis of survival status versus dioxin levels found no difference in the mean 1987 dioxin levels between 968 Ranch Hands who were still alive and the 23 Ranch Hands who were deceased as of 31 December 1993. There also was no relation between survival time and 1987 dioxin levels.

Further analysis was performed and reported in a 1998 journal article (11) describing the mortality of AFHS veterans. In particular, in the subgroup of Ranch Hand veterans that had survived more than 20 years since their military service in SEA, no increase in the risk of death due to cancer at all sites was found. When investigating cancer deaths according to primary anatomic site, a small increase in the number of deaths caused by cancer of the bronchus and lung was seen.

6.11 MORTALITY THROUGH 1999

As described in a journal article published in 2005 (12), as of 31 December 1999, 186 Ranch Hands and 2,330 Comparisons had died. The risk of death caused by cancer was not increased, but the risk of death caused by circulatory system diseases was increased in enlisted groundcrew. When circulatory disease was divided into five categories—atherosclerotic heart disease, cardiomyopathy, cerebrovascular disease, hypertensive disease, and other circulatory diseases—the strongest association between group and circulatory system disease was because of atherosclerotic heart disease. The cumulative all-cause mortality experience of Ranch Hands was not statistically greater than Comparisons (relative risk=1.15, 95% confidence interval: (1.0, 1.3), but this trend bears further monitoring to confirm the increased risk suggested by these results.

To examine cancer mortality in a way that accounts for latency, the risk was evaluated among those subjects who survived at least 20 years after entry into follow-up. No differences were found in this subset, as was also the case with cancer mortality within 20 years of service in SEA.

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7 CARDIOVASCULAR ASSESSMENT

7.1 INTRODUCTION

Cardiac disease and peripheral vascular disease are not recognized sequelae of exposure to phenoxy herbicides, chlorophenols, or dioxin. Both bradycardia and tachycardia have been suggested following acute heavy exposures to the 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) components, but the cardiovascular effects after chronic low-dose exposure are essentially unknown. To assess cardiovascular function and exposure to herbicides, the Air Force Health Study (AFHS) collected data by questionnaire and physical examination to identify a number of cardiac endpoints.

Analyses were performed to assess the cardiovascular function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). The analyses of the cardiovascular assessment were based on medical records verification of the data collected from questionnaires and the physical examination findings.

The questionnaire captured data on the occurrence of heart conditions. Medical records reviews confirmed reported heart conditions and identified any unreported conditions for each participant. As a result, a history of essential hypertension, heart disease (excluding essential hypertension), myocardial infarction, and stroke or transient ischemic attack was determined for each participant.

The physical examination assessed the central cardiac function by measurements of systolic blood pressure, diastolic blood pressure, heart sounds (by auscultation), and an electrocardiograph (ECG). The standard 12-lead ECG was performed and rhythm strips were obtained for all participants. The ECG findings were analyzed at each of the six physical examinations. The following components of the ECG have been analyzed since the 1985 follow-up examination: (1) right bundle branch block (RBBB), (2) left bundle branch block, (3) nonspecific ST- and T-wave changes, (4) bradycardia (a resting pulse rate less than 50 beats per minute), (5) tachycardia (a resting pulse rate greater than 100 beats per minute), (6) arrhythmia, (7) evidence of a prior myocardial infarction, and (8) other diagnoses (ventricular aneurysm and Wolff-Parkinson-White syndrome).

The peripheral vascular function was assessed during the cardiovascular examination by funduscopic examination of small vessels of the eyes, the presence or absence of carotid bruits, and the examination of the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. In 1982, 1985, and 1987, manual techniques were used to examine peripheral pulses. In 1985, the Doppler technique also was introduced to make these measurements and replaced the manual method for the 1992 through 2002 examinations.

The Doppler procedure for examining pulses involved a set of measurements designed to determine whether a pulse abnormality existed, where the obstruction was most likely located, and whether it had functional implications. Pulses were considered abnormal if no arterial flow or a monophasic arterial flow was present on either side.

In addition, two pulse indices were constructed from the radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulse measurements, as follows:

- Peripheral pulses: radial, femoral, popliteal, dorsalis pedis, and posterior tibial pulses

- Leg pulses: femoral, popliteal, dorsalis pedis, and posterior tibial pulses.

In addition, the assessment of all pulses combined the carotid pulse with peripheral pulses and was analyzed for the 1982, 1985, and 1987 examinations. Each of these indices was considered normal if all components were normal, and abnormal if one or more pulses were abnormal.

Other measurements to assess the peripheral vascular function included a measure of intermittent claudication and vascular insufficiency based on participant responses in the health questionnaire; a kidney, urethra, and bladder (KUB) x-ray assessment; a resting blood pressure index; and two hyperemic indices used as measures of intermittent claudication.

As a self-reported assessment of claudication, each participant was asked the following questions as part of the questionnaire:

- Do you get a pain in either or both of your legs while walking?
- Does this pain ever begin when you are standing still or sitting?
- Do you get this pain in either or both of your calf muscles?

The answers were used to detect intermittent claudication and vascular insufficiency (yes, no), which indicate an insufficient oxygen supply to the leg muscles. A participant was judged to have intermittent claudication and vascular insufficiency if he answered “yes” to the first and third questions and “no” to the second question. This self-reported determination of intermittent claudication was analyzed for the 1992, 1997, and 2002 follow-up examinations.

At the 1992 follow-up examination, a KUB x-ray assessment was accomplished to detect hardening of the arteries and vascular disease. Kidney stones, as detected from this assessment, were analyzed separately in the renal assessment, but if other abnormalities existed, the KUB x-ray assessment was defined as abnormal.

Three indices of claudication using peripheral blood pressure measurements were analyzed at the 2002 follow-up examination. Right and left brachial (upper arm) blood pressures were taken during the vascular examination using the Doppler technique. After brachial pressures were recorded, the right and left supine ankle pressures were measured. A resting pressure index was calculated from the resting ankle systolic pressure and the brachial systolic pressure. Post-exercise pressures were obtained at the ankle and the brachial arteries at the site of the highest pressures before exercise. Brachial and ankle pressures were obtained at 1 minute post-exercise and 2 minutes post-exercise, and two hyperemic pressure indices of claudication were calculated from these measurements after exercise.

The first Institute of Medicine (IOM) *Veterans and Agent Orange* report in 1994 (8) concluded that there is “inadequate or insufficient” evidence to establish an association between dioxin exposure and the occurrence of specific circulatory disorders, including coronary artery disease, myocardial infarction, stroke and hypertension, or circulatory diseases in general. The findings remained unchanged in all subsequent *Veterans and Agent Orange* updates (9-13).

7.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized,

particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this stratification based on the participant's tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the cardiovascular assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
All Pulses	X	X	X	X			
Carotid Bruits	X	X	X	X	X	X	X
Diastolic Blood Pressure	X	X	X	X	X	X	X
Dorsalis Pedis Pulses	X	X	X	X	X	X	X
ECG: Arrhythmia		X	X	X	X	X	X
ECG: Bradycardia		X	X	X	X	X	X
ECG: Evidence of Prior Myocardial Infarction					X	X	X
ECG: LBBB		X	X	X	X	X	X
ECG: Nonspecific ST- and T-wave Changes		X	X	X	X	X	X
ECG: Other Diagnoses		X	X	X	X	X	X
ECG: Overall	X	X	X	X	X	X	X
ECG: RBBB		X	X	X	X	X	X
ECG: Tachycardia		X	X	X	X	X	X
Essential Hypertension		X	X	X	X	X	X
Femoral Pulses	X	X	X	X	X	X	X
Funduscopy Examination	X	X	X	X	X	X	X
Heart Disease (Excluding Essential Hypertension)	X	X	X	X	X	X	X
Heart Sounds	X	X	X	X	X	X	X
Hyperemic Pressure Index (1 minute post-exercises)							X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Hyperemic Pressure Index (2 minutes post-exercise)							X
Intermittent Claudication and Vascular Insufficiency Index					X	X	X
KUB X-ray Assessment (Excluding Kidney Stones)					X		
Leg Pulses	X	X	X	X	X	X	X
Myocardial Infarction		X	X	X	X	X	X
Peripheral Pulses	X	X	X	X	X	X	X
Popliteal Pulses	X	X	X	X	X	X	X
Posterior Tibial Pulses	X	X	X	X	X	X	X
Radial Pulses	X	X	X	X	X	X	X
Resting Pressure Index							X
Stroke or Transient Ischemic Attack						X	X
Systolic Blood Pressure	X	X	X	X	X	X	X

7.2 ESSENTIAL HYPERTENSION

The prevalence of essential hypertension after service in Southeast Asia (SEA) increased as 1987 dioxin levels increased, based on data collected at the 1992 follow-up examination and again on data collected at the 1997 follow-up examination.

7.3 HEART DISEASE (EXCLUDING ESSENTIAL HYPERTENSION)

The prevalence of heart disease after service in SEA was increased in Ranch Hands based on data at the 1985 follow-up examination.

The prevalence of heart disease after service in SEA, based on data collected at the 1997 follow-up examination, was increased in Ranch Hands and, in particular, in Ranch Hand enlisted flyers. In addition, Ranch Hands in the background dioxin category had a greater prevalence of heart disease than Comparisons.

Ranch Hand enlisted flyers had a greater prevalence of heart disease after service in SEA than Comparison enlisted flyers, based on data collected at the 2002 follow-up examination.

7.4 MYOCARDIAL INFARCTION

Among participants with a low differential cortisol response, Ranch Hands in the low dioxin category had a greater prevalence of myocardial infarction after service in SEA than Comparisons, based on data collected at the 1987 follow-up examination.

The analysis of myocardial infarction after service in SEA, based on data collected at the 1992 follow-up examination, found that among nonobese (approximate body mass index less than 30) participants, Ranch Hands in the high dioxin category had a greater prevalence of myocardial infarction than Comparisons.

7.5 SYSTOLIC BLOOD PRESSURE

Among participants with type B personalities (14) who had later tours of duty, the percentage of participants with abnormally high systolic blood pressure values (>140 mm Hg) at the 1987 follow-up examination increased with increasing 1987 dioxin levels. In addition, the analysis showed that among younger participants, Ranch Hands in the low dioxin category had a greater prevalence of abnormally high systolic blood pressure values than Comparisons.

7.6 DIASTOLIC BLOOD PRESSURE

Among the youngest participants, Ranch Hands had a higher average diastolic blood pressure than Comparisons at the 1987 follow-up examination. Among participants with type B personalities, diastolic blood pressure values increased with increasing initial dioxin levels. Among participants with type B personalities and a family history of heart disease, Ranch Hands in the low dioxin category had a higher average diastolic blood pressure than Comparisons. In addition, among participants with type B personalities and no family histories of heart disease, Ranch Hands in the high dioxin category had a greater average diastolic blood pressure than Comparisons.

Among officers, diastolic blood pressure values at the 1992 follow-up examination increased as initial dioxin levels increased.

Analysis of 2002 follow-up examination data showed that Ranch Hands in the high dioxin category had a greater percentage of participants with abnormal diastolic blood pressure readings (>90 mm Hg) than Comparisons.

7.7 ECG

7.7.1 Overall

Among participants with normal cholesterol levels (≤ 200 mg/dL) at the 1992 follow-up examination, the percentage of Ranch Hands with abnormal overall ECG results increased with increasing levels of initial dioxin, as well as with increasing levels of 1987 dioxin.

7.7.2 Arrhythmia

For participants with later tours of duty, the occurrence of arrhythmias increased as 1987 dioxin levels increased at the 1987 follow-up examination. The prevalence of arrhythmia increased with increasing initial dioxin levels for participants with type A personalities (14).

Among participants who had never smoked, the percentage of Ranch Hands at the 1992 follow-up examination with arrhythmias increased with increasing levels of initial dioxin and 1987 dioxin. Among participants with low high-density lipoprotein (HDL) cholesterol levels (0-35 mg/dL), Ranch Hands in the high dioxin category had a greater prevalence of arrhythmias than Comparisons.

7.7.3 Evidence of Prior Myocardial Infarction

Among nondiabetic Ranch Hands, the percentage of participants with evidence of a prior myocardial infarction at the 1992 follow-up examination, as determined from the ECG, increased with increasing initial dioxin. In addition, evidence of prior myocardial infarction in Ranch Hands increased with increasing 1987 dioxin levels.

The percentage of Ranch Hands at the 1997 follow-up examination with evidence of a prior myocardial infarction increased with increasing initial dioxin levels.

7.7.4 Bradycardia

Ranch Hand enlisted flyers at the 1992 follow-up examination had a greater occurrence of bradycardia than Comparison enlisted flyers. Ranch Hands in the background dioxin category had a greater prevalence of bradycardia than Comparisons, primarily among participants with type B personalities.

7.7.5 Tachycardia

Ranch Hands in the high dioxin category had a greater prevalence of tachycardia than Comparisons at the 1997 follow-up examination.

7.7.6 Right Bundle Branch Block (RBBB)

Among moderate lifetime smokers (no more than 10 pack-years), the prevalence of RBBB at the 1992 follow-up examination increased with increasing initial dioxin. Analysis of 1992 follow-up examination data also found that the percentage of Ranch Hands with RBBB increased with increasing 1987 dioxin levels.

7.7.7 Nonspecific ST- and T-Wave Changes

Based on data collected for the 1992 follow-up examination, the presence of nonspecific ST- and T-wave changes increased with increasing 1987 dioxin levels.

7.7.8 Other Diagnoses

Analyses for the 1987 and 1997 follow-up examinations showed Ranch Hands in the high dioxin category had a greater occurrence of other ECG diagnoses than Comparisons.

Among Ranch Hand enlisted flyers, the prevalence of other ECG diagnoses at the 1992 follow-up examination increased with increasing 1987 dioxin levels.

7.8 FUNDUSCOPIC EXAMINATION

The 1992 follow-up examination analysis showed that the percentage of Ranch Hands with an abnormal fundusoscopic examination increased with increasing 1987 dioxin levels.

7.9 CAROTID BRUITS

Among the heaviest drinkers throughout their lifetimes in the 1992 follow-up examination (greater than 40 drink-years), Ranch Hands in the background and high dioxin categories had a greater prevalence of carotid bruits than Comparisons.

7.10 PULSES

7.10.1 All Pulses/Peripheral Pulses

When examining all pulses collectively, analysis of data from the 1987 follow-up examination revealed interactions between initial dioxin and age as well as between 1987 dioxin and lifetime smoking history. The percentage of Ranch Hand pulse abnormalities increased with increasing initial dioxin, primarily among older participants. Among Ranch Hands who were the heaviest lifetime smokers (greater than 10 pack-years) with later tours of duty, the prevalence of pulse abnormalities increased with increasing 1987 dioxin. A greater percentage of pulse abnormalities was seen among Ranch Hands in the low dioxin category and Ranch Hands in the high dioxin category than among Comparisons.

For 1987 follow-up examination data, the analysis of all pulses collectively included the carotid pulse in addition to peripheral pulses (radial, femoral, popliteal, dorsalis pedis, and posterior tibial). Exclusion of carotid pulses from the determination did not change the results described above.

In addition, peripheral pulses were examined at the 1982 baseline examination. Ranch Hands at the 1982 baseline examination had a greater percentage of abnormal peripheral pulses than Comparisons.

Analysis of diabetics at the 1992 follow-up examination showed that the percentage of diabetic Ranch Hands with abnormal peripheral pulses increased with increasing 1987 dioxin levels among Ranch Hands with no family history of heart disease. In addition, a higher percentage of Ranch Hand diabetics in the high dioxin category than Comparisons had abnormal peripheral pulses.

7.10.2 Leg Pulses

Leg pulses (peripheral pulses, with the exception of the radial pulses) at the 1987 follow-up examination mirrored the analysis of all pulses and peripheral pulses. Interactions between initial dioxin and age, as well as between 1987 dioxin and lifetime smoking history, were found. A greater percentage of leg pulse abnormalities was seen among Ranch Hands in the low dioxin category and Ranch Hands in the high dioxin category than among Comparisons.

At the 1992 follow-up examination, analysis showed the prevalence of abnormal leg pulses in diabetic Ranch Hands in the high dioxin category was greater than diabetic Comparisons.

7.10.3 Femoral Pulses

Analysis of data from the 1987 follow-up examination showed that a greater percentage of Ranch Hands (in particular, Ranch Hands in the high dioxin category) had abnormal femoral pulses than Comparisons. In addition, among participants with type A personalities, the prevalence of femoral pulse abnormalities increased with increasing initial dioxin levels.

Ranch Hands in the low dioxin category had a greater prevalence of abnormal femoral pulses than Comparisons at the 1992 follow-up examination.

7.10.4 Popliteal Pulses

A greater percentage of Ranch Hands (in particular, Ranch Hands in the high dioxin category) than Comparisons had abnormal popliteal pulses at the 1992 follow-up examination. In addition, among officers, the prevalence of popliteal pulse abnormalities increased with increasing 1987 dioxin levels.

7.10.5 Dorsalis Pedis Pulses

Analysis of 1987 follow-up examination data showed that the prevalence of dorsalis pedis pulse abnormalities increased with increasing 1987 dioxin among Ranch Hands with later tours of duty. Similarly, the prevalence of dorsalis pedis pulse abnormalities increased as initial dioxin levels increased.

Among older participants and diabetic participants at the 1992 follow-up examination, Ranch Hands in the high dioxin category had a greater prevalence of dorsalis pedis pulse abnormalities than Comparisons.

7.10.6 Posterior Tibial Pulses

Ranch Hands had a greater percentage of posterior tibial pulse abnormalities than Comparisons at the 1985 follow-up examination, as measured by manual palpation rather than Doppler methods.

The 1987 follow-up examination analysis found that Ranch Hands in the low dioxin category had a higher prevalence of abnormal posterior tibial pulses than Comparisons.

A greater percentage of Ranch Hands in the high dioxin category had posterior tibial pulse abnormalities than Comparisons at the 1992 follow-up examination. In addition, among moderate current cigarette smokers (no more than 20 cigarettes per day, on average), Ranch Hands in each of the dioxin categories (background, low, and high) had a greater percentage of posterior tibial pulse abnormalities at the 1992 follow-up examination than Comparisons.

7.11 KIDNEY, URETHRA, AND BLADDER (KUB) X-RAY ABNORMALITIES

Among non-Black participants, the percentage of Ranch Hands with KUB x-ray abnormalities at the 1992 follow-up examination increased with increasing 1987 dioxin levels.

7.12 AFHS CARDIOVASCULAR MORTALITY THROUGH 1999

As described in a 2005 article “Post-service Mortality of Air Force Veterans Occupationally Exposed to Herbicides during the Vietnam War” (15), as of 31 December 1999, 186 Ranch Hands and 2,330 Comparisons have died. The risk of death caused by circulatory system diseases was increased in enlisted groundcrew, which may suggest an association with dioxin. Of the 186 Ranch Hands who had died, 40 were enlisted groundcrew who had died from circulatory diseases. Of the 2,330 Comparisons who had died, 393 were enlisted groundcrew who had died from circulatory diseases.

7.13 CONCLUSION

After 25 years of observation in the AFHS, the prevalence of cardiovascular disease did not appear to be associated with dioxin exposure. Abnormal pulses appeared to be related to dioxin in earlier phases of the study, but not in the 2002 follow-up examination. The increase in the number of deaths caused by diseases of the circulatory system for Ranch Hand nonflying enlisted personnel, however, does point to the possibility of an association with dioxin.

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8 DERMATOLOGY ASSESSMENT

8.1 INTRODUCTION

The dermatology assessment of participants in the Air Force Health Study (AFHS) included the occurrence of self-reported acne and physical examination at the 1982, 1985, 1987, 1992, and 2002 examinations (1-6). Of particular interest was the detection of chloracne after exposure to herbicides and dioxin. Chloracne is recognized as a consequence of exposure to high levels of chlorophenols.

Chloracne may persist for at most 2 to 3 years. Therefore, primary lesions were not expected to be noted at the physical examinations. No biopsies to confirm the diagnosis of chloracne were deemed necessary by the examining dermatologists. Analysis was therefore limited to secondary lesions, such as scarring, hyperpigmentation, and depigmentation. If secondary lesions had been observed, chloracne might be suggested if the lesions had been found in the typical distribution areas of chloracne. In addition, the occurrence, duration, and location of acne were studied because of the absence of chloracne in AFHS veterans. This was the only objective way to assess for potential cases of chloracne.

During the health interview conducted as part of the questionnaire, each study participant was asked about occurrences of acne on the face since the date of the last health interview. This information was used to update data gathered from previous examinations. Information regarding the date and location of each acne occurrence also was collected. The analysis of acne was based on participant-reported occurrences rather than data from medical records verification because it was expected that the majority of participants who reported acne did not visit a physician for the acne.

Questions regarding the presence of acne emphasized acne on the temples, eyes, or ears, as acne on these locations may have been related to chloracne. Total duration of acne was determined by adding the duration of each reported occurrence of acne from all AFHS questionnaires. A review of medical records did not find any documented cases of chloracne among AFHS participants.

Six dermatologic conditions noted at the physical examination and a composite dermatologic index were analyzed. The following conditions were analyzed: acneiform lesions, acneiform scars, comedones, inclusion cysts, depigmentation, and hyperpigmentation of the skin. Depigmentation and hyperpigmentation were defined as areas of skin that were less or more pigmented relative to the rest of the skin. The dermatology index was created by combining results from the examination for comedones, acneiform lesions, acneiform scars, and inclusion cysts.

Other dermatologic evaluation abnormalities were analyzed as a group for the 1982, 1985, 1987, and 1992 physical examinations. The types of abnormalities are given in Section 8.6 of this chapter.

Some possible neoplasms were discovered by the physicians at the physical examinations. Contingent upon participant authorization, suspicious skin lesions were biopsied and the pathology determined. Abnormalities relating to skin malignancies are discussed in Chapter 14, Neoplasia Assessment.

The article written by AFHS authors, titled "Serum dioxin, chloracne, and acne in veterans of Operation Ranch Hand," studied the relation between categorized dioxin and the prevalence of acne for participants who attended the 1992 follow-up examination (7). None of the Ranch Hand veterans was diagnosed with chloracne and, therefore, analyses were restricted to acne. Acne was investigated both with and without

regard to anatomic location. No meaningful or consistent association between dioxin exposure and prevalence of acne was observed. Results suggested that exposure of Ranch Hand veterans to dioxin was insufficient for the production of chloracne, or perhaps the exposure may have caused chloracne that resolved and currently was undetectable.

In the 1994 *Veterans and Agent Orange* report published by the Institute of Medicine (IOM), the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides concluded that there is sufficient evidence of an association between exposure to dioxin and chloracne (8). This conclusion remained unaltered in the 2002 and 2004 IOM *Veterans and Agent Orange* updates (9, 10); however, the committee added a notation in this report that chloracne would appear shortly after dioxin exposure and not after a long latency (9).

8.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this stratification based on the participant's tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the dermatology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Acne - Self-reported Occurrence and Duration)	X	X	X	X	X	Analysis not performed	X
Acneiform Lesions	X	X	X	X			X
Acneiform Scars	X	X	X	X			X
Any Dermatologic Evaluation Abnormality	X						
Comedones	X	X	X	X			X
Depigmentation		X	X	X			X
Dermatology Index	X	X	X	X	X		X
Duration of Acne	X	X	X				X
Hyperpigmentation	X	X	X	X			X
Inclusion Cysts	X	X	X	X			X
Location of Post-SEA Acne (excluding participants with pre-SEA acne)		X	X	X	X		X
Other Dermatologic Evaluation Abnormalities	X	X	X	X	X		

8.2 ACNE – SELF-REPORTED OCCURRENCE AND DURATION

The occurrence, location, and duration of acne were reported by the participants at each physical examination and combined to construct a lifetime history of acne. Based on the compilation of all examinations, the analyses performed for the 2002 follow-up examination showed that the occurrence of reported acne after service in Southeast Asia (SEA) increased in Ranch Hand enlisted groundcrew, the subgroup with the highest median dioxin levels. The occurrence and duration of reported acne since SEA service increased in the background, low, and high Ranch Hand dioxin categories. In examining whether the occurrence of acne prior to service in SEA had an effect, it was discovered that the associations with dioxin were found only in participants who did not report acne prior to service in SEA. No relation was found in participants who did report acne prior to service in SEA.

8.3 ACNEIFORM LESIONS

The prevalence of acneiform lesions at the 2002 follow-up examination was greater for Ranch Hands in the background dioxin category than for Comparisons.

8.4 ACNEIFORM SCARS

As 1987 dioxin levels increased in Ranch Hands with later tours of duty, the occurrence of acneiform scars at the 1987 follow-up examination increased.

8.5 HYPERPIGMENTATION

Among older participants, the prevalence of hyperpigmentation at the 1987 follow-up examination increased as initial dioxin levels increased. In addition, as 1987 dioxin levels increased in Ranch Hands with later tours of duty, the occurrence of hyperpigmentation at the 1987 follow-up examination increased.

8.6 OTHER DERMATOLOGIC EVALUATION ABNORMALITIES

An endpoint named “other abnormalities,” which was the combination of vitiligo, jaundice, spider angiomas, palmar erythema, palmar keratosis, actinic keratosis, petechia, ecchymosis, conjunctival abnormality, oral mucosal abnormality, fingernail abnormality, toenail abnormality, dermatographia, cutis rhomboidalis, nevus, and other nonspecific abnormalities, was created for the purpose of analysis for the 1992 follow-up examination. This variable was considered abnormal if at least one of the above conditions was present and normal if all of the conditions were absent. For participants who reported acne prior to their tour of duty in SEA, the percentage of participants who had these other abnormalities increased as initial dioxin increased.

8.7 DERMATOLOGY INDEX

A dermatology index was created by combining results for comedones, acneiform lesions, acneiform scars, and inclusion cysts. A participant was defined as abnormal for this dermatology index if any of these conditions was present and defined as normal if none was present. Younger Ranch Hands in the background dioxin category had an abnormal dermatology index more often than younger Comparisons in the analysis of data collected at the 1992 follow-up examination.

8.8 CONCLUSION

Chloracne is a skin condition recognized as a consequence of exposure to high levels of dioxin and other cyclic organochlorine compounds. It usually appears without long latency after a short interval of exposure to dioxin and persists for about 2 to 3 years. Primary lesions of chloracne were not expected to persist and be noted upon physical examination. Chloracne might be suggested if the secondary lesions such as scarring, hyperpigmentation, and depigmentation had been observed in the typical distribution areas of chloracne around eyes, temples, and ears. No evidence of chloracne was found.

The dermatology assessment included the occurrence of self-reported acne and physical examination. An increased frequency of reported acne after service in SEA in Ranch Hand enlisted groundcrew was observed, along with an increase between the occurrence and duration of reported acne since SEA service in the background, low, and high Ranch Hand dioxin categories. The association between the occurrence and frequency of dioxin were found only in participants who did not report acne prior to service in SEA. No associations were found in participants who did report acne prior to service in SEA.

The interpretation of the increased frequency of reported acne after service in SEA in Ranch Hand enlisted groundcrew was observed, but is of uncertain meaning because secondary lesions that were observed revealed no association with herbicide or dioxin exposure.

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9 ENDOCRINOLOGY ASSESSMENT

9.1 INTRODUCTION

The human endocrine system generally is not believed to be a primary target of dioxin or dioxin-like exposure, although large doses of dioxin are known to produce a variety of metabolic phenomena in a number of species of experimental animals. Several sites of endocrine activity, including the pancreas, thyroid gland, and hypothalamic-pituitary-testis axis have been evaluated for dioxin toxicity in animal and human studies. Special emphasis has been placed on the parameters associated with diabetes in the Air Force Health Study (AFHS), due to the associations found in the analysis of the 1987, 1992, 1997, and 2002 follow-up examinations.

The two most important hormones secreted by the pancreas are insulin and glucagon. Insulin stimulates liver cells to take up glucose from the blood and convert it into glycogen. Glucagon stimulates the conversion of glycogen into glucose, which is then released into the blood. The production of insulin is regulated by blood glucose concentrations; high blood glucose concentrations combined with insulin deficiency results in diabetes. Type 2 diabetes, the diagnosis given to approximately 90 percent of all diabetes cases in the general population, describes a combination of insulin resistance, insulin deficiency, and glucose overproduction. The epidemiologic studies suggest that any increased risk of type 2 diabetes from herbicide or dioxin exposure is small when compared to known risk factors, such as family history, obesity, and physical inactivity.

The thyroid gland produces thyroxine (T_4) and triiodothyronine (T_3), hormones that are released in response to thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland. To maintain thyroid hormone homeostasis, the pituitary is stimulated to release more TSH when circulating T_3 and T_4 levels are low. Conversely, high levels of circulating T_3 and T_4 trigger the pituitary to reduce TSH production. Disruptions in this feedback loop can lead to diseases such as hypothyroidism and hyperthyroidism.

The hypothalamic-pituitary-testis axis produces several hormones affecting gonadal function. The hypothalamus releases gonadotropin-releasing hormone that subsequently signals the pituitary to release luteinizing hormone (LH), the hormone that regulates growth and development of eggs and sperm. Within the testis, LH stimulates testosterone production in the Leydig cells. Testosterone from the testes, as well as follicle-stimulating hormone (FSH) released by the pituitary, stimulates production of sperm. Excess testosterone converts to estradiol by the aromatase enzyme. Male-mediated adverse reproductive effects can be due to any number of imbalances in gonadal hormones produced via the hypothalamic-pituitary-testis axis.

The AFHS endocrinology assessment for the 1982, 1985, 1987, 1992, 1997, and 2002 follow-up examinations (1-7) included medical records verification of questionnaire responses, physical examination results, and laboratory findings.

The AFHS health interview questionnaires posed a general screening question on thyroid function and disease. Each participant was asked the following question during the in-person health interview: "Since the date of the last interview, has a doctor told you for the first time that you had thyroid problems?" Medical records review was accomplished to confirm self-reported problems with thyroid function and to

identify any unreported thyroid conditions. At each physical examination, a history of thyroid disease was constructed for each participant.

Similar information was asked of each participant regarding diabetes. This information also was verified and combined with previously collected information. For the 2002 follow-up examination, the American Diabetes Association's (ADA) revised definition of a diabetic was used (8). According to the ADA, a diabetic was defined as an individual with a 2-hour postprandial glucose level of 200 mg/dL or greater on two separate occasions, or a fasting glucose level of 126 mg/dL or greater on two separate occasions, or one 2-hour postprandial glucose level of 200 mg/dL or greater and a fasting glucose level of 126 mg/dL or greater on separate occasions. In addition, any participant diagnosed as a diabetic prior to the 2002 examination was included in the analysis.

Participants were considered diabetics at previous AFHS examinations if they had a 2-hour postprandial glucose level of 200 mg/dL or greater at that physical examination or a verified history of diabetes prior to that examination.

As part of the health interview questionnaire, questions were asked of diabetics regarding the use of insulin, oral diabetes medication, and diet. This self-reported information was verified and a diabetic control index was constructed and analyzed for all participants. This index was categorized as "requiring insulin," "oral hypoglycemics," "diet and exercise," or "no treatment" for diabetics and "no diabetes" for nondiabetics.

A variable that was termed "time to diabetes onset" was analyzed. This variable combined both diabetics and nondiabetics. For the purposes of statistical analyses, time to diabetes onset was the number of years between the date of diagnosis of diabetes and the end date of the last qualifying tour of duty in Southeast Asia (SEA) for diabetics. For nondiabetics, this variable was the number of years between the date of the AFHS physical examination and the end date of the last qualifying tour of duty in SEA.

The physical examination of endocrine function included manual palpation of the thyroid gland and testes. Thyroid abnormalities consisted of enlarged gland, tenderness, presence of nodules, or a thyroidectomy. Testicular abnormalities consisted of atrophied or testes surgically removed after SEA. Testicular volume (minimum and total) was determined using ultrasound techniques for the 1992 follow-up examination. Diabetic retinopathy and neuropathy (presence or absence) also were assessed for the 1992 follow-up examination.

Laboratory measurements for anti-thyroid antibodies (presence or absence), TSH (μ IU/mL), free T_4 (ng/dL), T_4 (μ g/dL), T_3 uptake (percent), total testosterone (ng/dL), free testosterone (pg/mL), LH (mIU/mL), FSH (mIU/mL), estradiol (pg/mL), glucagon (pg/mL), and sex hormone-binding globulin (SHBG) (nmol/L) were collected and analyzed for all participants in the endocrinology assessment. A free thyroxine index, which is a mathematical computation from T_4 and T_3 uptake that estimates how much thyroid hormone is free in the blood stream to work on the body, and a total testosterone to SHBG ratio were analyzed for the 1982 and 1992 AFHS examinations, respectively.

Glucose (mg/dL), urinary glucose (presence or absence), and serum insulin (μ IU/mL) (fasting for all participants and 2-hour postprandial for nondiabetics) were analyzed. Participants classified as diabetic were tested for hemoglobin A1c (percent), C-peptide (ng/mL), proinsulin (pmol/L), and glutamic acid decarboxylase antibodies (GADA) (presence or absence).

Two cortisol measurements, taken 2 hours apart, were obtained from all participants at the 1985 follow-up examination as a general indicator of the integrity of the endocrine system and as a secondary risk

factor for coronary heart disease. The two measurements, as well as the difference between the measurements, were analyzed.

The following journal articles on diabetes and glucose control were written by AFHS staff and their colleagues:

- Diabetes versus dioxin body burden in veterans of Operation Ranch Hand (9)
- Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand (10) and a follow-up letter to the editor (11)
- Letter to the Editor: Weight history, glucose intolerance, and insulin levels in middle-aged Swedish men (12)
- Serum dioxin, insulin, fasting glucose and sex hormone-binding globulin in veterans of Operation Ranch Hand (13)
- Serum dioxin level in relation to diabetes mellitus among Air Force veterans with background levels of exposure (14)
- Dioxin and diabetes mellitus: An analysis of the combined NIOSH and Ranch Hand data (15)
- Diabetes mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin elimination in veterans of Operation Ranch Hand (16)
- Insulin sensitivity following Agent Orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (17).

The following journal article on the thyroid function was written by AFHS staff and their colleagues:

- Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) levels and thyroid function in Air Force veterans of the Vietnam War (18).

The following journal articles on testosterone, FSH, LH, testicular abnormalities, sperm count, sperm abnormalities, and testicular volume were written by AFHS staff and their colleagues:

- Serum dioxin, testosterone, and gonadotropins in veterans of Operation Ranch Hand (19)
- [Follow-up] Letter to the editor (20).

These articles are discussed later in this chapter.

Based on a comprehensive review of the literature, the 2000 Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides found limited or suggestive evidence of an association between exposure to herbicides, including 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its contaminant dioxin, and type 2 diabetes (21). A separate report also was written describing the findings between type 2 diabetes and herbicide and dioxin exposure (22). This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (23).

In 2002, the IOM (24) concluded that there is inadequate or insufficient evidence to determine if an association exists between Agent Orange and other herbicides used in Vietnam and altered thyroid function. This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (23).

Based on the 2004 *Veterans and Agent Orange* update (23), “the lack of data on the association between exposure to the chemicals of interest and altered sperm characteristics or infertility, coupled with the lack

of exposure information on Vietnam veterans, precludes quantification of any possible increase in their risk.”

9.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this stratification based on the participant’s tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the endocrinology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
2-hour Cortisol		X					
2-hour Postprandial Glucose	X	X	X	X	X	X	X
2-hour Postprandial Urinary Glucose					X	X	X
Anti-thyroid Antibodies					X	X	X
C-peptide					X		X
Diabetes		X	X	X	X	X	X
Diabetic Control					X	X	X
Diabetic Neuropathy					X		
Diabetic Retinopathy					X		
Differential Cortisol		X					
Estradiol					X	X	X
Fasting Glucose				X	X	X	X
Fasting Urinary Glucose					X	X	

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Free T ₄							X
Free Testosterone					X	X	X
Free Thyroxine Index	X						
FSH			X	X	X	X	X
GADA							X
Glucagon					X		
Hemoglobin A1c					X	X	X
Initial Cortisol		X					
Insulin					X	X	X
LH					X	X	X
Proinsulin					X		X
SHBG					X		
T ₃ Uptake	X	X	X	X			
T₄	X				X	X	
Testicular Examination		X	X	X		X	X
Testicular Volume (Minimum and Total)					X		
Thyroid Disease		X	X	X	X	X	X
Thyroid Gland		X	X	X	X	X	X
Time to Diabetes Onset					X	X	X
Total Testosterone	X	X	X	X	X	X	X
Total Testosterone to SHBG Ratio					X		
TSH		X	X	X	X	X	X

Because of the nature of the endocrine function, this chapter has been organized into three sections: diabetes and glucose control, thyroid gland, and hypothalamic-pituitary-testis axis.

9.2 DIABETES AND GLUCOSE CONTROL

9.2.1 Prevalence of Diabetes

A higher percentage of Ranch Hands in the high dioxin category than Comparisons were diabetic in the analysis of the 1987 follow-up examination data. This difference was seen primarily in older participants. The percentage of diabetic Ranch Hands also increased with increasing initial and 1987 dioxin levels.

Among officers, the analysis of the 1992 follow-up examination data showed a higher prevalence of diabetes among Ranch Hands in the combined low and high dioxin category than Comparisons. The prevalence of Ranch Hand diabetics also increased with increasing initial dioxin and 1987 dioxin levels.

A higher percentage of Ranch Hands in the high dioxin category than Comparisons were diabetic at the 1997 follow-up examination. The prevalence of Ranch Hand diabetics also increased with increasing initial dioxin and 1987 dioxin levels.

In the analysis of the 2002 follow-up examination data, the percentage of participants classified as diabetic increased as initial and 1987 dioxin levels increased.

9.2.2 Diabetic Control

Analysis of 1992 follow-up examination data showed that the percentage of Ranch Hands using oral hypoglycemics to control diabetes increased with increasing initial dioxin levels and with 1987 dioxin levels, particularly among enlisted flyers and enlisted groundcrew. Ranch Hands in the high dioxin category had a higher prevalence of oral hypoglycemic use for diabetes than Comparisons. The percentage of Ranch Hands controlling diabetes through diet only increased with increasing 1987 dioxin levels, particularly among officers and enlisted flyers.

The percentage of Ranch Hands requiring insulin to control diabetes was greater than Comparisons in the analysis of the 1997 follow-up examination data. The percentage of Ranch Hands in both the low and high dioxin categories requiring insulin for diabetic control also was greater than Comparisons. The percentage of Ranch Hands requiring insulin increased with increasing initial dioxin levels. In addition, the percentage of Ranch Hands using diet only to control diabetes and the percentage of Ranch Hands using oral hypoglycemics for diabetic control increased with increasing 1987 dioxin levels.

Analysis of the 2002 follow-up examination data showed that the percentage of Ranch Hands requiring insulin increased with increasing initial and 1987 dioxin levels. A higher percentage of Ranch Hands in the high dioxin category than Comparisons required insulin. In addition, the percentage of Ranch Hands using oral hypoglycemics for diabetic control increased with increasing 1987 dioxin levels.

9.2.3 Time to Diabetes Onset

The analysis of 1992 follow-up examination data found that the time to diabetes onset decreased (adverse effect) with increasing 1987 dioxin levels. The time to diabetes onset decreased with increasing initial and 1987 dioxin levels in the 1997 and 2002 follow-up examination data analyses.

9.2.4 Fasting Glucose

In the analysis of the 1987 follow-up examination data, fasting glucose levels in Ranch Hands increased with increasing initial and 1987 dioxin levels. Similarly, the percentage of Ranch Hands with abnormally high fasting glucose levels increased with increasing initial dioxin and with 1987 dioxin levels. The average fasting glucose level was greater for Ranch Hands in the high dioxin category than for Comparisons, as was the prevalence of abnormally high fasting glucose levels.

The 1992 follow-up examination showed that fasting glucose levels in Ranch Hands increased with increasing initial dioxin, particularly among officers and enlisted groundcrew. Among only nondiabetic participants, fasting glucose levels increased with increasing initial dioxin among Ranch Hand officers. Fasting glucose levels increased with increasing 1987 dioxin when evaluating all Ranch Hands and also when analysis was restricted to only diabetic Ranch Hands. In addition, the prevalence of abnormally high fasting glucose levels in Ranch Hands increased with increasing 1987 dioxin. Nondiabetic Ranch Hands in the background dioxin category had a higher average fasting glucose level than nondiabetic Comparisons among enlisted groundcrew.

Fasting glucose levels and the prevalence of Ranch Hands with abnormally high fasting glucose levels increased with increasing initial dioxin and 1987 dioxin in the analysis of the 1997 follow-up examination data.

9.2.5 2-hour Postprandial Glucose

In the analysis of the 1987 follow-up examination data, 2-hour postprandial glucose levels in Ranch Hands increased with increasing initial dioxin levels and with 1987 dioxin levels in Ranch Hands with earlier tours. In addition, abnormally high 2-hour postprandial glucose levels were more prevalent among Ranch Hands in the high dioxin category than among Comparisons.

The analysis of 1992 follow-up examination data showed that Ranch Hands had higher average 2-hour postprandial glucose levels than Comparisons among obese (approximate body mass index of 30 or more) participants, among obese enlisted groundcrew, and among enlisted groundcrew with no family history of diabetes. Ranch Hands in the high dioxin category had higher average 2-hour postprandial glucose levels than Comparisons among obese participants and among participants with no family history of diabetes. A greater percentage of Ranch Hands in the high dioxin category than Comparisons also had elevated 2-hour postprandial glucose levels.

Two-hour postprandial glucose levels at the 1992 follow-up examination increased with increasing initial dioxin levels. An increase in 2-hour postprandial glucose levels with increasing 1987 dioxin levels was observed, as was the prevalence of elevated 2-hour postprandial glucose among non-Black participants.

9.2.6 Fasting Urinary Glucose

The analysis of the 1992 follow-up examination data showed that the percentage of Ranch Hands with fasting urinary glucose present increased with increasing initial dioxin and with 1987 dioxin, both when all participants were considered and when diabetic participants only were considered.

In the analysis of the 1997 follow-up examination data, the percentage of participants with fasting urinary glucose present increased with increasing 1987 dioxin.

9.2.7 2-hour Postprandial Urinary Glucose

Based on the analysis of the 1992 follow-up examination data, the prevalence of abnormal 2-hour postprandial urinary glucose levels in Ranch Hands increased with increasing 1987 dioxin levels.

Among officers, a higher percentage of Ranch Hands than Comparisons had 2-hour postprandial urinary glucose present at the 1997 and 2002 follow-up examination.

9.2.8 Insulin

Based on the analysis of all participants, the 1992 follow-up examination data analysis showed a higher average insulin level in Ranch Hands than in Comparisons among obese participants and obese officers. Insulin levels in Ranch Hands increased with increasing 1987 dioxin levels. The prevalence of abnormally high insulin levels was greater in Ranch Hands than in Comparisons among obese officers and among obese participants in the background dioxin category.

The 1992 follow-up examination analysis of diabetic participants showed that the average serum insulin level was higher for Ranch Hands in the low dioxin category than for Comparisons. Among older diabetic participants, the prevalence of abnormally high insulin levels was higher for Ranch Hands in the low dioxin category than for Comparisons.

The 1992 follow-up examination analysis of nondiabetic participants showed a higher average serum insulin level for Ranch Hands than Comparisons among obese participants. Serum insulin levels for

nondiabetic Ranch Hand participants increased with increasing initial and 1987 dioxin levels. The prevalence of abnormally high serum insulin levels in Ranch Hands increased with increasing 1987 dioxin and also increased with increasing initial dioxin levels, particularly among enlisted flyers. Also among enlisted flyers, Ranch Hands in the high dioxin category had a higher prevalence of abnormally high serum insulin levels than Comparisons.

Data for both fasting (for all participants) and 2-hour postprandial insulin (for nondiabetics) were collected for the 2002 follow-up examination data. Fasting insulin levels and the prevalence of abnormally high fasting insulin levels increased in Ranch Hands as initial dioxin increased. Ranch Hand enlisted groundcrew had a lower average 2-hour postprandial insulin level than Comparison enlisted groundcrew.

9.2.9 Hemoglobin A1c

Hemoglobin A1c indicates a patient's blood sugar control over the last 2 to 3 months. Hemoglobin A1c is formed when glucose in the blood binds irreversibly to hemoglobin to form a stable glycated hemoglobin complex and is not subject to the fluctuations that are seen with daily blood glucose monitoring.

Hemoglobin A1c levels increased with increasing initial dioxin levels among Ranch Hand officers and enlisted groundcrew in the analysis of the 1992 follow-up examination data. The percentage of Ranch Hand officers with abnormally high hemoglobin A1c levels also increased with increasing initial dioxin levels. In addition, an increase in hemoglobin A1c levels with increasing 1987 dioxin levels was observed among all Ranch Hands, older obese Ranch Hands, and diabetic Ranch Hands. Among obese Ranch Hands, the prevalence of abnormally high hemoglobin A1c levels increased with increasing 1987 dioxin levels.

Ranch Hands in the high dioxin category had increased average hemoglobin A1c levels and a greater prevalence of abnormally high hemoglobin A1c levels than Comparisons when the 1997 follow-up examination data were analyzed. In addition, hemoglobin A1c levels increased with increasing 1987 dioxin levels in Ranch Hands, and the percentage of Ranch Hands with abnormally high hemoglobin A1c levels increased with increasing 1987 dioxin levels.

In the analysis of the 2002 follow-up examination data, the prevalence of abnormally high hemoglobin A1c levels in Ranch Hand diabetics increased with increasing 1987 dioxin levels.

9.2.10 C-peptide

C-peptide is a subunit of insulin and is measured to differentiate insulin production by the body and insulin injected into the body. The C-peptide level may be measured in a patient with type 2 diabetes to see if any insulin is still being produced by the body. It may also be measured in the evaluation of low blood sugar to see if too much insulin is being produced by a patient.

The analysis of the 1992 follow-up examination data showed that Ranch Hands in the low dioxin category had a higher average C-peptide level than Comparisons among diabetic enlisted groundcrew. In addition, Ranch Hands in the low dioxin category had a greater prevalence of abnormally high C-peptide levels than Comparisons, primarily among older diabetic participants.

9.2.11 Glucagon

In the 1992 follow-up examination data analysis, serum glucagon levels increased in Ranch Hands as 1987 dioxin increased, particularly among Ranch Hands with no family history of diabetes. The percentage of Ranch Hands with an abnormally high glucagon level also increased as 1987 dioxin increased. Among all participants who treat their diabetes through diet only, and among officers who do the same, Ranch Hands had a higher average serum glucagon level than Comparisons when diabetic participants were analyzed separately. When nondiabetics were analyzed separately, serum glucagon levels increased in Ranch Hands as initial and 1987 dioxin levels increased.

9.2.12 Proinsulin

Proinsulin is a precursor of insulin with minimal hormonal activity and is converted into insulin by enzymatic action.

The 1992 follow-up examination analysis of diabetic Ranch Hands showed that the percentage of Ranch Hand officers with abnormally high serum proinsulin levels increased with increasing 1987 dioxin levels.

9.2.13 Diabetes Versus Dioxin Body Burden in Veterans of Operation Ranch Hand

An analysis based on veterans who participated in the 1987 physical examination and who had a dioxin measurement was conducted to investigate glucose intolerance and diabetes versus dioxin levels (9). A history of diabetes, time to diabetes onset, and how diabetes is being treated or controlled were analyzed versus dioxin. Associations with initial dioxin were observed for fasting glucose and diabetes. Both associations were consistent with a dose-response effect. An effect also was present between diabetes and categorized dioxin and between time to diabetes onset and categorized dioxin, consistent with a dose-response effect within Ranch Hands. Ranch Hands in the high dioxin category experienced diabetes sooner than Comparisons. A greater percentage of Ranch Hands in the high dioxin category required diet control, oral medications, or insulin to treat their diabetes than Comparisons.

9.2.14 Serum Dioxin and Diabetes Mellitus in Veterans of Operation Ranch Hand

The prevalence of diabetes, use of oral medications to control diabetes, and time-to-diabetes onset were studied, based on participants who had a dioxin measurement and attended the 1982, 1985, 1987, or 1992 AFHS examination (10). Analysis was also conducted on glucose levels and serum glucose abnormalities based on participants at the 1992 physical examination who had a dioxin measurement. Each Ranch Hand veteran was assigned to the background, low, or high dioxin exposure category on the basis of a measurement of dioxin body burden. Glucose abnormalities, diabetes prevalence, and the use of oral medications to control diabetes increased, and time-to-diabetes-onset decreased, with dioxin exposure. Serum insulin abnormalities for Ranch Hands in the high dioxin category were increased in nondiabetics. The results indicated a possible relation between dioxin exposure and diabetes mellitus, glucose metabolism, and insulin production.

Subsequent to the publication of the above article, the possibility of an interaction between plasma lipid fractions, diabetes, and total serum dioxin levels was raised. The concern was that dioxin may be more heavily concentrated in the triglyceride fraction of total lipids, which would contribute to the finding of increased risk of diabetes mellitus in participants with high dioxin levels because diabetes is associated with increased triglycerides. The AFHS authors conducted further analysis and found no evidence to support concern (11).

9.2.15 Letter to the Editor: Weight History, Glucose Intolerance, and Insulin Levels in Middle-aged Swedish Men

A 1998 article described the relation between impaired glucose tolerance and type 2 diabetes mellitus and the length of time that a subject had been overweight (25). Duration of overweight was studied as an independent risk factor for impaired glucose tolerance and type 2 diabetes mellitus using data from the 1992 AFHS follow-up examination (12). The relation of body mass index and waist circumference to risk of impaired glucose tolerance or diabetes mellitus generally agreed between the two articles. Duration of being overweight, however, was not seen as an independent risk factor.

9.2.16 Serum Dioxin, Insulin, Fasting Glucose and Sex Hormone-Binding Globulin in Veterans of Operation Ranch Hand

Insulin, fasting glucose, and SHBG were analyzed in relation to dioxin based on participants at the 1992 physical examination who had a dioxin measurement (13). Each Ranch Hand veteran was assigned to one of three dioxin categories—background, low, and high—based on his dioxin level. Among nondiabetic veterans, insulin was increased for Ranch Hands in the high dioxin category. Insulin decreased as SHBG increased among young (age 53 or less), lean (body mass index < 30), nondiabetic veterans in the high category. The findings suggest a compensatory metabolic relation between dioxin and insulin regulation.

9.2.17 Serum Dioxin Level in Relation to Diabetes Mellitus among Air Force Veterans with Background Levels of Exposure

Data from several epidemiologic studies suggest that exposure to unusually high amounts of dioxin increases the risk of diabetes mellitus, and experimental data suggest that the mechanism for this is decreased cellular glucose uptake. To investigate the dose response relation more closely, the association of serum dioxin level with prevalence of diabetes mellitus and with levels of serum insulin and glucose was examined among 1,197 veterans in the AFHS who never had contact with dioxin-contaminated herbicides and whose serum dioxin level was within the range of background exposure typically seen in the United States (≤ 10 ng/kg lipid) (14). The prevalence of diabetes was increased for those veterans who were in the highest quartile of dioxin levels (≥ 5.2 ng/kg lipid), as compared to veterans in the first quartile of dioxin levels (< 2.8 ng/kg lipid). The association was slightly weaker after adjusting for serum triglycerides drawn at the same time of the dioxin measurement. A positive relation existed between glucose and insulin levels and serum dioxin; adjustment for serum triglycerides again weakened most of the associations. Whether adjustment for serum triglycerides was appropriate, however, could not be determined with the available data. The association of background-level dioxin exposure with the prevalence of diabetes in these data may well be due to reasons other than causality, although a causal contribution cannot be wholly dismissed.

9.2.18 Dioxin and Diabetes Mellitus: An Analysis of the Combined NIOSH and Ranch Hand Data

In an attempt to reconcile disparate results, analysis was conducted in a similar manner from combined AFHS and National Institute for Occupational Safety and Health (NIOSH) data sets, the two principal studies of dioxin and diabetes. A uniform approach to outcome definition, data analysis, and covariate control was adopted, and results were described in a 2001 journal article (15). This article reanalyzed data from 990 Ranch Hands and 1,275 Comparisons and a NIOSH population of 267 chemical workers and 227 referents. The Ranch Hand veterans had lower concentrations of lipid-adjusted serum dioxin (median 12 parts per trillion [ppt]) than the NIOSH workers (median 75 ppt). The combined exposed groups did not differ markedly from the combined nonexposed groups for prevalence of diabetes, with no

evidence of a difference of exposure effect between studies. In addition, virtually no difference was found between combined exposed and nonexposed groups in average fasting serum glucose, and there was little evidence in either study of a dose-response trend for fasting serum glucose. An increasing trend was found in prevalence of diabetes with increased dioxin among the Ranch Hand population, with excess risk largely confined to the highest 8 percent of the exposed group (>78 ppt serum dioxin) versus those with less than 10 ppt dioxin. No such positive dose-response was found in the NIOSH population. The reason for the difference in diabetes dose-response trends between the two studies was unknown.

Reviewers of AFHS results on diabetes hypothesized that the association between diabetes and dioxin concentration reflects an association between diabetes and the dioxin elimination rate. Individuals with slow elimination rates may retain dioxin for a longer period of time, have a long dioxin half-life, and, consequently, may be at an increased risk for diabetes. Individuals with quick elimination rates may retain dioxin for a shorter period of time, have a relatively short dioxin half-life, and may be at a decreased risk for diabetes.

9.2.19 Diabetes Mellitus and 2,3,7,8-tetrachlorodibenzo-p-dioxin Elimination in Veterans of Operation Ranch Hand

Results of AFHS analyses to examine this hypothesis were reported in a 2003 journal article (16). No relation was found between the rate of dioxin elimination and the occurrence or time to onset of diabetes. Without adjustment for age, body mass index, family history of diabetes, and smoking history, the time to onset of diabetes decreased and the risk of diabetes increased with a diminished elimination rate. After adjustment for age, body mass index, family history of diabetes, and smoking history, diabetes time to onset and occurrence were not associated with dioxin elimination. No difference was found between the average elimination rates of diabetic and nondiabetic veterans, without or with adjustment for risk factors.

9.2.20 Insulin Sensitivity Following Agent Orange Exposure in Vietnam Veterans with High Blood Levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin

Studies to determine whether insulin sensitivity was related to dioxin were performed and reported in a 2004 journal article (17). Ranch Hand and Comparison subjects were matched by age, body mass index, race, and a family history of diabetes. Insulin sensitivity was measured using a frequently sampled intravenous glucose tolerance test in a matched study of 29 Ranch Hand-Comparison pairs of veterans and a quantitative insulin sensitivity check index based on fasting glucose and fasting insulin in 71 matched pairs. There were no differences in an insulin sensitivity index, a quantitative insulin sensitivity check index, tumor necrosis factor alpha (TNF α), adiponectin, and two measures of insulin secretion between Ranch Hands and Comparisons. The difference in the insulin sensitivity index and the quantitative insulin sensitivity check index between the Ranch Hand member and the Comparison member of the pair decreased as the difference in dioxin increased. These data suggested that high blood dioxin levels may promote an insulin-resistant state, but the magnitude of this effect appeared to be small, such that an 18-fold increase in dioxin due to increased exposure resulted in only a 10 percent change in the insulin sensitivity index in the 29 matched pairs.

9.3 THYROID

9.3.1 Thyroid Disease

In the 1992 follow-up examination analysis of thyroid disease, among participants with type A personalities (26), a higher percentage of Ranch Hands in the background dioxin category had a history of thyroid disease than Comparisons.

9.3.2 Anti-thyroid Antibodies

Ranch Hands in the combined low and high dioxin category had a higher prevalence of anti-thyroid antibodies than Comparisons, based on analysis of the 1992 follow-up examination data.

9.3.3 Thyroid-stimulating Hormone (TSH)

A higher average TSH level in Ranch Hands than Comparisons was observed at the 1985 follow-up examination.

Ranch Hands in the high dioxin category had a higher average TSH level than Comparisons at the 1987 follow-up examination.

Based on data from the 1997 follow-up examination, a greater percentage of Ranch Hand enlisted groundcrew than Comparison enlisted groundcrew had an abnormally high TSH value.

The analysis of the 2002 follow-up examination data showed that the average TSH level was higher for Ranch Hands than Comparisons, primarily among officers. Ranch Hands in the background dioxin category also had a higher average TSH level than Comparisons.

9.3.4 Thyroxine (T₄)

In the analysis of the 1992 follow-up examination data, the percentage of abnormally high T₄ levels increased with increasing initial and 1987 dioxin levels.

9.3.5 Serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Levels and Thyroid Function in Air Force Veterans of the Vietnam War

Potential health effects of dioxin concentration on total T₄, TSH, T₃ uptake, the free thyroxine index, and thyroid diseases were examined in an AFHS article published in 2003 (18). Data for 1,009 Ranch Hand and 1,429 Comparison veterans compliant to any of the AFHS examinations in 1982, 1985, 1987, 1992, and 1997 were analyzed. Each veteran was assigned to one of four dioxin categories: Comparison, background Ranch Hand, low Ranch Hand, or high Ranch Hand. The 1982, 1985, 1987, 1992, and 1997 AFHS examinations showed a trend of increasing TSH that was not accompanied by changes in circulating T₄ or in the percentage of T₃, which was measured only in 1982 and 1985. Ranch Hands in the low and high dioxin categories had a greater TSH average than Comparisons, and a trend test showed a linear increase across the Comparison, background, low, and high dioxin categories. There was no evidence of changes in clinical thyroid disease, and no changes in microsomal or anti-thyroidal antibodies were observed. These findings suggest that dioxin may affect thyroid hormone metabolism and function in Ranch Hand veterans.

9.4 HYPOTHALAMIC-PITUITARY-TESTIS AXIS

9.4.1 Differential Cortisol

Younger Black Ranch Hands had a lower mean differential cortisol level than their Comparison counterparts at the 1985 follow-up examination.

9.4.2 Testicular Examination

In the analysis of the 1987 follow-up examination data, the percentage of Ranch Hands with an abnormal testicular examination increased with increasing initial and 1987 dioxin levels. In addition, more Ranch Hands in the high dioxin category had an abnormal testicular examination than Comparisons.

9.4.3 Testicular Volume (Minimum and Total)

In the 1992 follow-up examination data analysis, the minimum testicular volume, using ultrasound techniques, decreased as 1987 dioxin levels increased among Ranch Hand enlisted flyers. Total testicular volume, using ultrasound techniques, decreased with increasing levels of initial and 1987 dioxin among Ranch Hand enlisted flyers.

9.4.4 Total Testosterone

The analysis of the 1987 follow-up examination data found that testosterone levels decreased (adverse effect) with increasing 1987 dioxin levels in Ranch Hands with later tours of duty. Testosterone levels also decreased with increasing initial dioxin levels, particularly among Ranch Hands with type A personalities. In addition, Ranch Hands in the high dioxin category had a lower average testosterone level than Comparisons. Among participants with type A personalities, the prevalence of abnormally low testosterone levels was greater in Ranch Hands in the high dioxin category than in Comparisons.

In the analysis of 1992 follow-up examination data, testosterone levels decreased with increasing 1987 dioxin among all Ranch Hands, and among officers and enlisted flyers, in particular. Among Ranch Hands with type A personalities, testosterone levels decreased with increasing initial dioxin levels. The percentage of Ranch Hand officers with abnormally low testosterone levels increased as initial and 1987 dioxin levels increased. In addition, among participants with type A personalities, Ranch Hands in the background and low dioxin categories had a greater percentage of abnormally low testosterone levels than Comparisons.

9.4.5 Free Testosterone

In the 2002 follow-up examination data analysis, Ranch Hand officers were found to have had a higher percentage of abnormally low free testosterone levels than Comparison officers.

9.4.6 Estradiol

The analysis of the 1992 follow-up examination data found that the percentage of abnormally high estradiol levels increased with increasing 1987 dioxin levels among Ranch Hand enlisted groundcrew.

9.4.7 Follicle-stimulating Hormone (FSH)

The 1987 follow-up examination data analysis showed that FSH levels increased with increasing 1987 dioxin levels among Ranch Hands with later tours of duty. In the analysis of the 1992 follow-up examination data, a higher percentage of Ranch Hand officers had abnormally high FSH levels relative to Comparison officers.

9.4.8 Luteinizing Hormone (LH)

The percentage of Ranch Hands at the 1992 follow-up examination with abnormal high LH levels increased with increasing initial dioxin levels. In addition, Ranch Hands in the low dioxin category had a higher average LH level than Comparisons.

In the analysis of 2002 follow-up examination data, Ranch Hand officers had a higher average LH level than Comparison officers. Ranch Hands in the low dioxin category also had a higher average LH level than Comparisons.

9.4.9 Serum Dioxin, Testosterone, and Gonadotropins in Veterans of Operation Ranch Hand

Using data from the 1982, 1987, and 1992 examinations, the relations between dioxin and current testosterone, FSH, LH, testicular abnormalities, sperm count, sperm abnormalities, and testicular volume were studied (19). No consistent or meaningful association between dioxin levels and any of these outcome variables were found. The authors noted that, if adverse effects did exist, the Ranch Hand exposure in Southeast Asia was insufficient to produce detectable associations comparable with those seen in industrial workers with heavier exposure.

Reviewers of the aforementioned article commented that analyses on testosterone, FSH, and LH in their continuous form were not mentioned. In a follow-up letter to the editor (20), the AFHS authors confirmed that analyses had been conducted. Findings from these analyses were weak and inconsistent with known exposure differences in Ranch Hands by military occupation. The authors noted that there may be a subclinical relation between dioxin and testosterone but the association, if it exists, was too weak to be clinically meaningful.

9.5 CONCLUSION

Results from the 1987, 1992, 1997, and 2002 follow-up examinations showed a consistent and potentially meaningful adverse relation between dioxin levels and diabetes. Although the prevalence of diabetes was comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism showed the possibility of adverse effects from dioxin in relation to glucose intolerance and insulin production. A dioxin-related increase in severity, a decrease in the time from exposure to first diagnosis, and an increase in fasting glucose and hemoglobin A1c supported the dioxin relation with the occurrence of diabetes. Increased risks of diabetes were found with initial dioxin, in the high dioxin category, and with 1987 dioxin levels. An increase in severity, a decrease in the time from exposure to first diagnosis, and an increase in fasting glucose and hemoglobin A1c also were observed as initial and 1987 dioxin levels increased.

Sporadic associations between dioxin levels and thyroid or gonadal hormone abnormalities appeared unlikely to be clinically important.

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10 GASTROINTESTINAL ASSESSMENT

10.1 INTRODUCTION

There is a wealth of dioxin research data available in animal models, but there is relatively little information about the effects of dioxin on the human digestive system. The liver is a major target organ for dioxin and dioxin-like chemicals following single high-dose and continued low-dose exposure in laboratory animals. Porphyria cutanea tarda (PCT) is a suspected clinical endpoint following moderate to high level exposure. Although the discussions in this chapter deal with the gastrointestinal function, the focus of the chapter is on liver function and associated diseases.

Analyses were performed in the gastrointestinal assessment of Air Force Health Study (AFHS) participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7), based on medical records verification of the data collected from questionnaires, physical examination, and laboratory findings. During the health interviews for each AFHS examination, each participant was asked about the occurrence of hepatitis, jaundice, cirrhosis, enlarged liver, and other liver conditions. Medical records reviews confirmed reported conditions and identified any unreported conditions for each participant. Data from all AFHS examinations were combined to form a history of liver conditions for each participant. These verified results were grouped into the following eight categories of disorders for analysis: (1) uncharacterized hepatitis (non-A, non-B, and non-C), (2) jaundice (unspecified, not of the newborn), (3) chronic liver disease and cirrhosis (alcohol-related), (4) chronic liver disease and cirrhosis (nonalcohol-related), (5) liver abscess and sequelae of chronic liver disease, (6) enlarged liver (hepatomegaly), (7) acute and subacute necrosis of the liver, and (8) other disorders of the liver. The purpose of the uncharacterized hepatitis (non-A, non-B, and non-C) category was to define a category that was neither clearly A nor B nor C, so that liver disease misdiagnosed as “viral hepatitis” could be detected.

During the administration of the questionnaire, each participant was asked the following three questions: (1) “Have you had patches of your skin change color?”; (2) Have you had easier bruising of the skin than usual?”; and (3) “Have you had skin that was extra sensitive or seemed to hurt for no reason?” Participant-reported responses to these questions on skin bruises, patches, or sensitivity were analyzed. Positive responses to the presence of skin bruises, patches, or sensitivity were considered as a surrogate measure for a possible symptom of PCT. This variable was analyzed at the 1982, 1985, and 1987 follow-up examinations.

The presence of gastric, duodenal, peptic, or gastrojejunal ulcers, as verified by a review of medical records, was analyzed.

Current hepatomegaly was assessed by the AFHS examining physician.

Laboratory variables analyzed included alanine aminotransferase (ALT in U/L), aspartate aminotransferase (AST in U/L), gamma glutamyltransferase (GGT in U/L), alkaline phosphatase (U/L), creatine phosphokinase (U/L), total bilirubin (mg/dL), direct bilirubin (mg/dL), lactate dehydrogenase (LDH in U/L), cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), cholesterol-HDL ratio, triglycerides (mg/dL), stool hemocult, prothrombin time (seconds), serum amylase (U/L), and 10 components (in mg/dL) in a protein profile (prealbumin, albumin, α -1-acid glycoprotein, α -1-

antitrypsin, α -2-macroglobulin, apolipoprotein B, C3 complement, C4 complement, haptoglobin, and transferrin).

Serological evidence of prior hepatitis A, B, C, and D, as well as current hepatitis B infection, were analyzed.

Analyses were conducted and described for d-glucaric acid, which is considered to be a reliable index of hepatic microsomal activity. The analyses were based on urine collected at the 1985 follow-up examination and stored at -70 °C.

PCT is a disorder of porphyrin metabolism that leads to massive overproduction and excretion of uroporphyrin. Uroporphyrin and coproporphyrin were analyzed, as was d-aminolevulinic acid, the first compound in the porphyrin synthesis pathway.

The following journal article on the relation of hepatic abnormalities and indices of hepatic function to dioxin was written by AFHS staff and their colleagues:

- Dioxin and hepatic abnormalities in veterans of Operation Ranch Hand (8).

This article is discussed later in this chapter.

The Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides reported in their 1994 publication, *Veterans and Agent Orange* (9), that there was “sufficient” evidence to establish an association between PCT and herbicides or dioxin, although not a causal relation. In the 1996 *Veterans and Agent Orange* update, the association with PCT was changed to “limited or suggestive” (10). This was also the conclusion in the 2004 *Veterans and Agent Orange* update (11).

10.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at

most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this stratification based on the participant’s tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the gastrointestinal assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Acute and Subacute Necrosis of the Liver			X	X	X	X	X
Albumin					X	X	X
Alkaline Phosphatase	X	X	X	X	X	X	X
ALT	X	X	X	X	X	X	X
Apolipoprotein B					X	X	X
AST	X	X	X	X	X	X	X
C3 Complement					X	X	X
C4 Complement					X	X	X
Cholesterol	X	X	X	X	X	X	X
Cholesterol-HDL Ratio			X	X	X	X	X
Chronic Liver Disease and Cirrhosis (Alcohol-related)	X	X	X	X	X	X	X
Chronic Liver Disease and Cirrhosis (Nonalcohol-related)	X	X	X	X	X	X	X
Coproporphyrin	X	X					
Creatine Phosphokinase			X	X	X	X	X
Current Hepatitis B						X	
Current Hepatomegaly	X	X	X	X	X	X	X
d-aminolevulinic acid	X						
d-glucaric acid				X			
Direct Bilirubin	X	X	X	X	X	X	X
Enlarged Liver (Hepatomegaly)		X	X	X	X	X	X
GGT	X	X	X	X	X	X	X
Haptoglobin					X	X	X
HDL Cholesterol			X	X	X	X	X
Jaundice (unspecified)	X	X	X	X	X	X	X
LDH	X	X	X	X	X	X	X
Liver Abscess and Sequelae of Chronic Liver Disease			X	X	X	X	X
Other Liver Disorders	X	X	X	X	X	X	X
Prealbumin					X	X	X
Prior Hepatitis A					X	X	X
Prior Hepatitis B					X	X	X
Prior Hepatitis C					X	X	X
Prior Hepatitis D						X	
Prothrombin Time				X	X	X	X
Serum Amylase					X	X	X
Skin Bruises, Patches, or Sensitivity	X	X	X	X			

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Stool Hemocult					X	X	X
Total Bilirubin	X	X	X	X	X	X	X
Transferrin					X	X	X
Triglycerides	X	X	X	X	X	X	X
Ulcer		X	X	X			
Uncharacterized Hepatitis	X	X	X	X	X	X	X
Uroporphyrin	X	X					
α-1-Acid Glycoprotein					X	X	X
α-1-Antitrypsin					X	X	X
α-2-Macroglobulin					X	X	X

10.2 HEPATITIS

10.2.1 Uncharacterized Hepatitis (Non-A, Non-B, Non-C)

Data from the 1987 follow-up examination showed an increase in the prevalence of uncharacterized hepatitis as initial dioxin levels increased and as 1987 dioxin levels increased (for those with earlier tours of duty). Ranch Hands in the high dioxin category also had a greater occurrence of uncharacterized hepatitis than Comparisons.

10.2.2 Prior Hepatitis B

Among enlisted flyers, the occurrence of prior hepatitis B infection at the time of the 1992 follow-up examination increased with increasing 1987 dioxin levels.

10.3 LIPIDS

10.3.1 Cholesterol

Ranch Hands at the 1987 follow-up examination showed an increase in cholesterol with increasing initial dioxin levels, as well as with increasing 1987 dioxin levels for those in earlier tours of duty. Ranch Hands in the high dioxin category had a greater average cholesterol level than Comparisons, and Ranch Hands in the background dioxin category had a greater percentage of abnormally high cholesterol values than Comparisons.

Among moderate lifetime drinkers (no more than 40 drink-years at the time of the examination), Ranch Hands in the background dioxin category had a greater average cholesterol value at the 1992 follow-up examination than Comparisons. Among lifetime nondrinkers, Ranch Hands in the high dioxin category had a greater average cholesterol value than Comparisons. Among Ranch who did not report exposure to degreasing chemicals, cholesterol values and the percentage of Ranch Hands with abnormally high cholesterol values increased with increasing initial dioxin levels.

Among heaviest current drinkers (more than four drinks per day) at the time of the 1992 follow-up examination, a greater percentage of Ranch Hands than Comparisons had abnormally high cholesterol values. Among the heaviest current drinkers, Ranch Hands in the background dioxin category had a greater percentage of abnormally high cholesterol values than Comparisons. Among moderate current drinkers (no more than four drinks per day), a greater percentage of Ranch Hands in the low dioxin

category than Comparisons had abnormally high cholesterol values. Cholesterol levels and the percentage of abnormally high cholesterol levels for Ranch Hands (in particular, Ranch Hand officers) at the 1992 follow-up examination increased with increasing 1987 dioxin levels.

10.3.2 High-density Lipoprotein (HDL) Cholesterol

Among Ranch Hands who did not report exposure to degreasing chemicals, HDL cholesterol at the 1987 follow-up examination decreased with increasing initial dioxin levels. HDL cholesterol levels decreased with increasing 1987 dioxin levels.

A greater percentage of Ranch Hands (primarily officers) at the 1992 follow-up examination had abnormally low HDL cholesterol values relative to Comparison officers. Among the heaviest lifetime drinkers (more than 40 drink-years prior to the 1992 examination), a greater percentage of Ranch Hands in the background dioxin category than Comparisons had abnormally low HDL cholesterol values.

Among moderate lifetime drinkers (no more than 40 drink-years prior to the 1992 examination), HDL cholesterol values at the 1992 follow-up examination decreased and the percentage of Ranch Hands with abnormally low HDL cholesterol values increased with increasing 1987 dioxin levels. Similarly, HDL cholesterol values decreased as 1987 dioxin levels increased among Ranch Hands who were light or moderate drinkers (more than four drinks per day) at the time of the 1992 examination.

As seen at the 1997 follow-up examination, a greater percentage of Ranch Hands in the background dioxin category than Comparisons had abnormally low HDL cholesterol values.

10.3.3 Cholesterol-HDL Ratio

Ranch Hands in the 1987 follow-up examination showed an increase in the cholesterol-HDL ratio with increasing initial dioxin levels. Ranch Hands in the high dioxin category had a greater average cholesterol-HDL ratio than Comparisons.

Ranch Hands with earlier tours of duty (in particular, those who did not report exposure to industrial chemicals) showed an increase in cholesterol-HDL ratio at the 1987 follow-up examination. The percentage of Ranch Hands with an abnormally high cholesterol-HDL ratio value also increased as 1987 dioxin levels increased. In addition, the percentage of abnormally high cholesterol-HDL ratio values among all Ranch Hands, among Ranch Hands who did not report exposure to degreasing chemicals, and among older Ranch Hands who did report exposure to degreasing chemicals, increased with increasing initial dioxin levels.

An increase in the cholesterol-HDL ratio, and an increase in the percentage of abnormally high cholesterol-HDL ratio values in Ranch Hands as 1987 dioxin levels increased, were observed at both the 1992 and 1997 follow-up examinations.

10.3.4 Triglycerides

Among the oldest participants in the 1985 follow-up examination, Ranch Hands had a greater average triglyceride value than Comparisons.

The 1987 follow-up examination showed that triglyceride values and the prevalence of abnormally high triglyceride values in Ranch Hands increased with increasing initial dioxin levels. Triglyceride values in Ranch Hands increased with increasing 1987 dioxin levels. The prevalence of abnormally high

triglyceride values also increased with increasing 1987 dioxin levels in Ranch Hands with later tours of duty.

Among officers, triglyceride values at the 1992 follow-up examination increased with increasing initial dioxin levels. As 1987 dioxin levels increased in Ranch Hands (as a group, and for officers who were moderate or heavy drinkers), an increase in triglyceride values was observed. In addition, an increase in the percentage of Ranch Hands with abnormally high triglyceride values was seen as 1987 dioxin levels increased. Ranch Hand officers had a greater average triglyceride value and a greater percentage of abnormally high triglyceride values than Comparison officers. Ranch Hands in the high dioxin category had a greater average triglyceride value and a greater percentage of abnormally high triglyceride values than Comparisons.

Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater occurrence of abnormally high triglyceride values than Comparison enlisted groundcrew. Ranch Hands in the high dioxin category had a greater average triglyceride value and a greater percentage of abnormally high triglyceride values than Comparisons. In addition, as 1987 dioxin levels increased, triglyceride values and the prevalence of abnormally high triglyceride values in Ranch Hands increased.

The 2002 follow-up examination found that Ranch Hands (primarily enlisted groundcrew) had a greater occurrence of abnormally high triglyceride values than Comparisons. Similarly, Ranch Hands in the low and high dioxin categories had a greater occurrence of abnormally high triglyceride values than Comparisons. An increase in the prevalence of triglyceride abnormalities in Ranch Hands also was seen as 1987 dioxin levels increased.

10.4 LIVER ENZYMES

10.4.1 Alanine Aminotransferase (ALT)

Ranch Hands (in particular, younger Ranch Hands) had increased ALT values at the 1987 follow-up examination with increasing initial dioxin levels. Among light alcohol drinkers (less than one drink per day) at the time of the 1987 examination and Ranch Hands who did not report exposure to degreasing chemicals, the percentage of abnormally high ALT values increased with increasing initial dioxin levels. In addition, among lighter alcohol drinkers at the time of the 1987 dioxin examination, ALT levels increased with increasing 1987 dioxin for Ranch Hands with earlier tours of duty. Ranch Hands in the high dioxin category had a greater average ALT value than Comparisons.

The analysis of ALT at the 1992 follow-up examination showed that ALT values in Ranch Hands and the percentage of Ranch Hands with abnormally high ALT values increased with increasing 1987 dioxin levels.

The 1997 follow-up examination analysis of ALT found that the percentage of Ranch Hands with abnormally high ALT values increased with increasing initial and 1987 dioxin levels. ALT values in Ranch Hands also increased with increasing 1987 dioxin levels. In addition, Ranch Hands in the low and high dioxin categories combined had a greater average ALT value than Comparisons.

10.4.2 Aspartate Aminotransferase (AST)

Among moderate alcohol drinkers at the 1985 follow-up examination (one to four drinks per day), Ranch Hands had a greater average AST value than Comparisons.

Among moderate drinkers at the time of the 1992 follow-up examination, AST values increased with increasing initial dioxin levels. Among heaviest drinkers at the time of the examination (more than four drinks per day), AST values increased with increasing initial dioxin levels and 1987 dioxin levels.

The 1997 follow-up examination analysis showed that AST values and the percentage of abnormally high AST values increased with increasing 1987 dioxin. In addition, Ranch Hands in the high dioxin category had a greater average AST value than Comparisons.

10.4.3 Gamma Glutamyltransferase (GGT)

GGT values at the 1987 follow-up examination increased with increasing initial dioxin levels. Similarly, the percentage of abnormally high GGT values increased with increasing initial dioxin levels for all Ranch Hands and specifically among Ranch Hands who did not report exposure to degreasing chemicals. Ranch Hands in both the low and high dioxin categories had a greater average GGT value and a greater prevalence of abnormally high GGT values than Comparisons. Among participants who did not report exposure to degreasing chemicals, a greater percentage of Ranch Hands in the high dioxin category than Comparisons had abnormally high GGT values. GGT values increased with increasing 1987 dioxin levels for Ranch Hands with later tours of duty.

Among Ranch Hands who did not report exposure to degreasing chemicals, GGT values at the 1992 follow-up examination increased with increasing initial dioxin. Also among participants who did not report exposure to degreasing chemicals, Ranch Hands in the high dioxin category had a greater average GGT value and a greater percentage of abnormally high GGT values than Comparisons. Ranch Hands (primarily officers and enlisted flyers) showed an increase in GGT values as 1987 dioxin levels increased. The percentage of abnormally high GGT values increased with increasing 1987 dioxin levels.

The 1997 follow-up examination found that Ranch Hands in the high dioxin category had a greater average GGT value than Comparisons. GGT values and the percentage of abnormally high GGT values in Ranch Hands increased with increasing 1987 dioxin levels.

10.4.4 Alkaline Phosphatase

Analysis of 1985 follow-up examination data found that Ranch Hands had a greater average alkaline phosphatase value than Comparisons. Among those participants who did not report exposure to industrial chemicals, Ranch Hands also had a greater average alkaline phosphatase value than Comparisons.

Ranch Hands at the 1987 follow-up examination (in particular, Ranch Hands in the high dioxin category) had a greater average alkaline phosphatase value than Comparisons. Black Ranch Hands also had a greater average alkaline phosphatase value than Black Comparisons. Alkaline phosphatase levels increased with increasing initial dioxin levels in Ranch Hands. In addition, the percentage of Ranch Hands with abnormally high alkaline phosphatase values increased with increasing 1987 dioxin among Ranch Hands with earlier tours of duty.

Among all participants, non-Black participants, younger participants, and participants who did not report exposure to degreasing chemicals, all Ranch Hands and Ranch Hand enlisted groundcrew had a greater average alkaline phosphatase value at the 1992 follow-up examination. Among all participants and those who did not report exposure to degreasing chemicals, Ranch Hands in the background dioxin category and Ranch Hands in the low dioxin category had a greater average alkaline phosphatase value than Comparisons.

In addition, Ranch Hand enlisted groundcrew had a greater percentage of abnormally high alkaline phosphatase values than Comparison enlisted groundcrew at the 1992 follow-up examination. Similarly, Ranch Hands in the background dioxin category had a greater percentage of abnormally high alkaline phosphatase values than Comparisons. Alkaline phosphatase levels increased with increasing 1987 dioxin levels among Black Ranch Hands.

The 1997 follow-up examination analysis found that for all participants and for enlisted groundcrew, Ranch Hands had a greater average alkaline phosphatase value than Comparisons. Ranch Hands in the background dioxin category also had a greater average alkaline phosphatase value than Comparisons.

Ranch Hand enlisted groundcrew at the 2002 follow-up examination had a greater percentage of abnormally high alkaline phosphatase values than Comparison enlisted groundcrew.

10.4.5 Creatine Phosphokinase

Ranch Hands at the 1992 follow-up examination showed an increase in creatine phosphokinase values as 1987 dioxin levels increased. Similarly, the 1997 follow-up examination analysis showed an increase in creatine phosphokinase values and an increase in the percentage of Ranch Hands with abnormally high creatine phosphokinase values as 1987 dioxin levels increased.

10.4.6 Direct Bilirubin

Analysis of 1985 follow-up examination data found that, among participants who did not report exposure to industrial chemicals, a greater percentage of Ranch Hands than Comparisons had abnormally high direct bilirubin values.

Ranch Hands at the 1987 follow-up examination showed an increase in direct bilirubin values with increasing initial dioxin levels. In addition, Ranch Hands in the high dioxin category had a greater average direct bilirubin value than Comparisons.

10.4.7 Lactate Dehydrogenase (LDH)

The 1992 follow-up examination analysis showed that, among enlisted groundcrew who were the heaviest lifetime drinkers (more than 40 drink-years at the 1992 follow-up examination), Ranch Hands had a greater average LDH value than Comparisons. Also among the heaviest lifetime drinkers, Ranch Hands in the background dioxin category had a greater percentage of abnormally high LDH values than Comparisons.

10.5 OTHER LIVER DISORDERS

A greater percentage of Ranch Hands in the high dioxin category than Comparisons had other liver disorders, based on data collected at the 1987 follow-up examination.

At the 1992 follow-up examination, other liver disorders among Ranch Hands increased with increasing initial and 1987 dioxin levels. Ranch Hands in the high dioxin category had a greater prevalence of other liver disorders than Comparisons.

The occurrence of other liver disorders increased with increasing initial dioxin levels, based on data collected at the 1997 follow-up examination. As in the 1987 and 1992 follow-up examinations, analysis

of 1997 follow-up examination data found that Ranch Hands in the high dioxin category had a greater prevalence of other liver disorders than Comparisons.

Subsequent analysis was conducted to investigate whether the findings for the occurrence of other liver disorders could be explained by a particular subcategory of liver disorders (12). Five separate subcategories were explored. Although the associations described above were found when the five subcategories were combined, no associations were observed when the subcategories were analyzed individually.

10.6 PROTEIN PROFILE

10.6.1 α -1-Acid Glycoprotein

Among lifetime nondrinkers through the 1992 follow-up examination, Ranch Hands in the low dioxin category had a greater average α -1-acid glycoprotein value than Comparisons. In addition, younger Ranch Hands in the low dioxin category had a greater percentage of abnormally high α -1-acid glycoprotein values than younger Comparisons. Ranch Hand enlisted flyers had an increase in the percentage of abnormally high α -1-acid glycoprotein values at the 1992 follow-up examination as both initial dioxin and 1987 dioxin levels increased.

Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater average α -1-acid glycoprotein value than Comparison enlisted groundcrew.

10.6.2 α -1-Antitrypsin

Ranch Hands in the background dioxin category had a greater average α -1-antitrypsin value than Comparisons, as seen at the 1992 follow-up examination. In addition, α -1-antitrypsin values in Ranch Hands decreased with increasing 1987 dioxin levels.

Analysis of data from the 1997 follow-up examination revealed that Ranch Hands and Ranch Hand enlisted groundcrew had a greater average α -1-antitrypsin value than their Comparison counterparts. Ranch Hands in both the background and high dioxin categories had a greater average α -1-antitrypsin value than Comparisons.

The 2002 follow-up examination analysis found that Ranch Hands in the low dioxin category had a greater percentage of abnormally high α -1-antitrypsin values than Comparisons.

10.6.3 α -2-Macroglobulin

Among older participants, α -2-macroglobulin values at the 1992 follow-up examination increased with increasing initial dioxin levels.

Ranch Hands at the 1997 follow-up examination showed an increase in the percentage of abnormally high α -2-macroglobulin values as 1987 dioxin levels increased.

10.6.4 Albumin

The 1992 follow-up examination of albumin found that among those who did not report exposure to industrial chemicals, Ranch Hands in the low dioxin category had a lower average albumin value (adverse effect) than Comparisons. Among heaviest drinkers at the time of the 1992 examination and among

participants who did not report exposure to degreasing chemicals, albumin decreased with increasing 1987 dioxin levels.

10.6.5 Apolipoprotein B

Among Ranch Hands (primarily older Ranch Hands), both apolipoprotein B values and the percentage of abnormally high apolipoprotein B values at the 1992 follow-up examination increased with increasing initial dioxin levels and 1987 dioxin levels.

10.6.6 C3 Complement

The 1992 follow-up examination analysis of C3 complement found that Ranch Hands in the background dioxin category had a lower average C3 complement value (adverse effect) than Comparisons.

10.6.7 C4 Complement

Ranch Hand officers at both the 1997 and 2002 follow-up examinations had a lower average C4 complement value (adverse effect) than Comparison officers. In addition, analysis of 2002 follow-up examination data indicated that the average C4 complement value decreased and the percentage of abnormally low C4 complement values increased with increasing initial dioxin.

10.6.8 Haptoglobin

For all participants and, specifically, among enlisted groundcrew, Ranch Hands had a greater average haptoglobin value than Comparisons at the 1992 follow-up examination. Among Ranch Hand officers, the percentage of abnormally high haptoglobin values increased with increasing initial dioxin levels.

Ranch Hands at the 1997 follow-up examination (in particular, enlisted groundcrew) had a greater average haptoglobin value than Comparisons. The percentage of abnormally high haptoglobin values was also greater for Ranch Hands than for Comparisons. Ranch Hands in the background dioxin category had a greater average haptoglobin value and a greater percentage of abnormally high haptoglobin values than Comparisons. In addition, Ranch Hands in the low and high dioxin categories combined had a greater average haptoglobin value than Comparisons.

As in the 1997 follow-up examination, Ranch Hands in the 2002 follow-up examination had a greater average haptoglobin value than Comparisons, particularly among enlisted groundcrew.

10.6.9 Prealbumin

Among participants who did not report exposure to degreasing chemicals, prealbumin values at the 1992 follow-up examination decreased (adverse effect) with increasing 1987 dioxin levels.

Ranch Hand enlisted groundcrew at the 1997 follow-up examination had a greater percentage of abnormally low prealbumin values than Comparison enlisted groundcrew. Similarly, Ranch Hands in the high dioxin category had a greater percentage of abnormally low prealbumin values than Comparisons.

10.7 PROTHROMBIN TIME

The 1987 follow-up examination of prothrombin time revealed an increase in prothrombin time as initial dioxin levels increased among Ranch Hands, and, in particular, among Ranch Hands who were moderate

lifetime smokers (no more than 10 pack-years). In addition, the 1987 follow-up examination found Ranch Hands with later tours of duty had an increased prevalence of prothrombin time abnormalities as 1987 dioxin levels increased.

As in the 1987 follow-up examination, the 1992 follow-up examination showed an increase in prothrombin time with increasing initial dioxin levels.

Ranch Hands in the background dioxin category had a higher average prothrombin time than Comparisons at the 2002 follow-up examination.

10.8 SKIN BRUISES, PATCHES, OR SENSITIVITY

The 1987 follow-up examination found that Ranch Hands in each of the background, low, and high dioxin categories had a greater occurrence of skin bruises, patches, or sensitivity than Comparisons.

10.9 STOOL HEMOCCULT

The 1992 follow-up examination showed that among the heaviest lifetime drinkers (in particular, officers and enlisted groundcrew), a greater percentage of Ranch Hands than Comparisons had positive stool hemoccult results. A greater percentage of Ranch Hands in the low dioxin category than Comparisons also had positive stool hemoccult results.

A greater percentage of Ranch Hand officers than Comparison officers had positive stool hemoccult results at the 2002 follow-up examination.

10.10 DIOXIN AND HEPATIC ABNORMALITIES IN VETERANS OF OPERATION RANCH HAND

The associations between hepatic abnormalities and indices of hepatic function and dioxin were published in a journal article appearing in the *Annals of Epidemiology* in 2001 (8). The prevalence of ever having liver disease through March 1993, and ALT, AST, GGT, LDH, alkaline phosphatase, and total bilirubin, were examined according to serum dioxin levels. Ranch Hand veterans with the highest dioxin exposure were more likely than Comparisons to have a history of abnormal serum enzyme levels and liver function tests. The liver disorders associated with dioxin exposure primarily reflected earlier increases in ALT (prior to the 1992 follow-up examination) and continued increased levels of GGT. Whether the associations observed were causal was unclear.

10.11 CONCLUSION

Analysis of laboratory data indicated that dioxin was associated with hepatic enzymes such as AST, ALT, and GGT, and with lipid-related health indices such as cholesterol, HDL, and triglycerides. Although hepatic enzymes showed an association with dioxin, there was no evidence of an increase in overt liver disease. These laboratory findings were consistent with significant associations seen for obesity-related variables in other clinical assessments, such as the body mass index results in the general health assessment and the diabetes and glucose results noted in the endocrinology assessment. These findings may represent a dioxin-mediated alteration of biochemical processes or a subtle relation between dioxin and lipid metabolism.

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11 GENERAL HEALTH ASSESSMENT

11.1 INTRODUCTION

Analyses were performed to assess the general health of Air Force Health Study (AFHS) participants at all six examinations (1-7). Measures of general health included an estimate of a participant's body fat; a participant-reported perception of his health; the appearance of the subject as younger than, older than, or the same as his stated age, as observed by a board-certified internist; and an appearance of illness or distress as observed by the internist. Clinicians often employ measures such as these to assess an overall state of health. While these measures may be imperfect and were no doubt influenced by many variables, they do reflect overall health impressions from both self and observer perspectives.

At each examination, a board-certified internist at the examination recorded the appearance of acute illness or distress (yes, no) of the AFHS participant. The appearance of illness was reserved for a relatively low percentage of participants who had significant manifestations of illness, such as cachexia and frailty. No associations between appearance of illness or distress and either group or dioxin levels were observed at the AFHS examinations.

11.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this stratification based on the participant's tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the general health assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Appearance of Illness or Distress	X	X	X	X	X	X	X
Body Mass Index/Body Fat	X	X	X	X	X	X	X
Relative Age Appearance as Assessed by a Physician	X	X	X	X	X	X	X
Self-perception of Health	X	X	X	X	X	X	X

11.2 BODY MASS INDEX/BODY FAT

Body fat measures and the commonly used body mass index are approximate measures of the percentage of a person's body mass that can be attributable to fat. The body mass index serves as a valuable clinical clue to the presence of disease and helps define obesity—an important health risk factor. The estimator of body fat and obesity for the AFHS has changed over the years but has always used the ratio of a person's weight to the square of his height.

The 1985 follow-up examination found that the average body fat was less for Ranch Hands than for Comparisons. Beginning with the dioxin measurements in 1987, analyses showed increased body fat with increasing dioxin within Ranch Hands. This relation was evident for initial dioxin, categorized dioxin, and 1987 dioxin. The same patterns with dioxin, particularly categorized dioxin and 1987 dioxin, were observed for the analyses of the 1992, 1997, and 2002 follow-up examination data. The average body mass index, however, was similar between Ranch Hands and Comparisons.

When the body fat measure or body mass index was categorized as obese (body mass index greater than 30 for the 2002 follow-up examination) or normal (less than 30), the same patterns were seen. Beginning with the dioxin measurements in 1987, analyses showed increasing obesity with dioxin within Ranch Hands. Similar patterns with dioxin, particularly categorized dioxin and 1987 dioxin, were observed for the analyses of the 1992, 1997, and 2002 follow-up examination data. The percentage of obese participants, however, was similar between Ranch Hands and Comparisons.

The association appears to be due to slower dioxin elimination pharmacokinetics in obese participants relative to participants who were lean or not obese. In part, participants with the highest dioxin levels retain dioxin due to their higher body fat content.

11.3 SELF-PERCEPTION OF HEALTH

During the health interview administered for all examinations, each AFHS participant was asked the following: "Compared to other people your age, would you say your health is excellent, good, fair, or poor?" This self-reported perception was analyzed as a measure of the general health status of each participant, although it was recognized that the perception was susceptible to varying degrees of conscious and subconscious bias (e.g., in 1992 and after, most participants were aware of their serum dioxin levels). This variable was dichotomized as excellent or good and fair or poor for analyses.

At the 1982 baseline examination, more Ranch Hands perceived their health to be fair or poor than Comparisons. This pattern was seen at the 1985, 1992, and 1997 follow-up examinations, with the largest difference among enlisted groundcrew. Differences between Ranch Hands and Comparisons were not observed at the 2002 follow-up examination.

Similar patterns were observed when examining the relation between self-perception of health and measures of dioxin. In 1987, 1992, and 1997, the percentage of participants perceiving their health as fair or poor increased with increased dioxin levels. An association between self-perception of health and measures of dioxin, however, was not observed at the 2002 follow-up examination.

11.4 RELATIVE AGE APPEARANCE AS ASSESSED BY A PHYSICIAN

At each examination, a board-certified internist noted the appearance of the subject as younger than, older than, or the same as his stated age. This variable was dichotomized as older than stated age and same as or younger than stated age for analyses. Because the examining internist was kept blind to the participant's group membership, this assessment was less subject to bias than the self-perception of health.

Ranch Hands appeared younger relative to their age more often than Comparisons at the 1982 baseline examination. At the 1992 follow-up examination, the percentage of Ranch Hand officers who appeared older relative to his age decreased as 1987 dioxin levels increased.

11.5 CONCLUSION

Body mass index was positively associated with 1987 dioxin, possibly reflecting the pharmacokinetics of dioxin elimination. More Ranch Hands perceived their health to be fair or poor than Comparisons and there was an increasing perception of fair or poor health with dioxin through the 1997 follow-up examination, but these differences were not observed for the 2002 follow-up examination.

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12 HEMATOLOGY ASSESSMENT

12.1 INTRODUCTION

Hematology is the study of the red blood cells, white blood cells, platelets, and plasma. These components perform important functions related to fighting infections, regulating temperature, transporting oxygen to other cells, and the balancing of body fluids. Scientific literature has not found any consistent relation between exposure to Agent Orange or dioxin and hematopoietic toxicity to date. The Air Force Health Study (AFHS) examined the basic components of the participants' blood at each of the six physical examinations (1-7).

A complete blood count was performed at the 1982, 1985, 1987, 1992, 1997, and 2002 AFHS examinations. Elements of the complete blood count that were analyzed were hematocrit, hemoglobin, platelet count, red blood cell (RBC) count, and white blood cell (WBC) count. Analysis also was performed on mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume for the 1982, 1985, and 1987 examinations. In addition, associations between group or dioxin and erythrocyte sedimentation rate were examined for all six AFHS examinations.

Analysis of a differential WBC count was performed for the 1992, 1997, and 2002 follow-up examinations, with the differential results reported as absolute counts. The absolute WBC counts of segmented neutrophils, neutrophilic bands, lymphocytes, monocytes, eosinophils, and basophils were analyzed. Lymphocytes included both reactive and nonreactive lymphocytes. RBC morphology was constructed from a number of laboratory findings, many of which were minor abnormalities, measured at these three AFHS examinations.

In addition, associations between group or dioxin and prothrombin time were investigated for the 1987, 1992, 1997, and 2002 follow-up examinations, and fibrinogen measurements were collected and analyzed for the 2002 follow-up examination.

The following journal article on the relation of indices of hematologic function and their relations to dioxin and herbicides was written by AFHS staff and their colleagues:

- Relation of serum 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) level to hematological examination results in veterans of Operation Ranch Hand (8).

This article is discussed later in this chapter.

12.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this stratification based on the participant's tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the hematology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Absolute Basophils					X	X	X
Absolute Eosinophils					X	X	X
Absolute Lymphocytes					X	X	X
Absolute Monocytes					X	X	X
Absolute Neutrophils (bands)					X	X	X
Absolute Neutrophils (segs)					X	X	X
Erythrocyte Sedimentation Rate	X	X	X	X	X	X	X
Fibrinogen							X
Hematocrit	X	X	X	X	X	X	X
Hemoglobin	X	X	X	X	X	X	X
Mean Corpuscular Hemoglobin	X	X	X	X			
Mean Corpuscular Hemoglobin Concentration	X	X	X	X			
Mean Corpuscular Volume	X	X	X	X			
Platelet Count	X	X	X	X	X	X	X
RBC Count	X	X	X	X	X	X	X
RBC Morphology					X	X	X
WBC Count	X	X	X	X	X	X	X

12.2 HEMATOCRIT

Ranch Hands with later tours of duty showed increased hematocrit values at the 1987 follow-up examination as 1987 dioxin increased.

12.3 HEMOGLOBIN

Analysis of 1987 follow-up examination data found that hemoglobin values for Ranch Hands with later tours of duty increased with increasing 1987 dioxin.

12.4 MEAN CORPUSCULAR HEMOGLOBIN

At the 1982 baseline examination, Ranch Hands had a higher average mean corpuscular hemoglobin value than did Comparisons.

12.5 MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION

At the 1987 follow-up examination, Ranch Hands in the background and low dioxin categories had a higher average mean corpuscular hemoglobin concentration than Comparisons.

12.6 MEAN CORPUSCULAR VOLUME

Ranch Hands had a greater mean corpuscular volume than Comparisons at the 1982 baseline examination. The 1987 follow-up examination found that among the heaviest lifetime smokers (>10 pack-years), the prevalence of mean corpuscular volume abnormalities increased with increasing initial dioxin levels. In addition, at the 1987 follow-up examination, Ranch Hands in the low dioxin category had a greater prevalence of abnormally high mean corpuscular volume levels than Comparisons.

12.7 PLATELET COUNT

For heavy smokers at the 1985 follow-up examination, Ranch Hands had a greater average platelet count than Comparisons.

Analysis performed for the 1987 follow-up examination showed that Ranch Hands had a greater average platelet count and a greater occurrence of abnormally high platelet counts than Comparisons. The differences were primarily in younger Ranch Hands and for Ranch Hands in the high dioxin category.

Ranch Hands had a greater average platelet count at the 1992 follow-up examination than Comparisons, with the difference in the platelet count averages occurring among enlisted participants rather than officers. In addition, Ranch Hands in the high dioxin category had a greater average platelet count and a greater prevalence of abnormally high platelet counts than Comparisons. The 1992 follow-up examination also found that the occurrence of abnormally high platelet counts increased with increasing 1987 dioxin levels.

The 1997 follow-up examination found the average platelet count was lower among Ranch Hands officers than Comparison officers and greater among Ranch Hand enlisted personnel than Comparison enlisted personnel. Ranch Hand officers also had a higher prevalence of abnormally low platelet counts than Comparison officers. Ranch Hands in the high dioxin category had a greater average platelet count than Comparisons.

Ranch Hand enlisted flyers had a greater average platelet count than Comparison enlisted flyers at the 2002 follow-up examination.

12.8 RBC COUNT

Analyses of RBC count performed for the 1987 follow-up examination found among older participants with earlier tours of duty, RBC counts decreased with increasing 1987 dioxin levels. Among younger participants with earlier tours of duty, however, RBC counts increased with increasing 1987 dioxin levels. In addition, for Ranch Hands with earlier tours of duty, the prevalence of abnormally low RBC counts increased with increasing 1987 dioxin levels.

The 1992 follow-up examination found that among the heaviest smoking officers (more than 20 cigarettes per day), Ranch Hands had a greater average RBC count than Comparisons. This difference was due primarily to heavy Ranch Hand smokers in the background dioxin category.

12.9 WBC COUNT

Younger Black officer and enlisted flyer Ranch Hands in the 1985 follow-up examination had lower average WBC counts than their Comparison counterparts. Younger non-Black heavy-smoking Ranch Hands had a greater average WBC count than younger non-Black heavy-smoking Comparisons.

A positive association was seen between initial dioxin and WBC count in the analysis of 1987 follow-up examination data. Ranch Hands in the high dioxin category also had a greater average WBC count than Comparisons. In addition, WBC counts increased with increasing 1987 dioxin levels. Among younger participants with earlier tours of duty, WBC counts also increased with increasing 1987 dioxin levels.

At the 1992 follow-up examination, Ranch Hands had lower average WBC counts than Comparisons among Black participants and among Black officers. Among Black participants and among officers, WBC counts increased with increasing initial dioxin levels. Similarly, WBC counts increased with increasing 1987 dioxin levels among Black participants.

WBC counts decreased with increasing 1987 dioxin levels based on the evaluation of 2002 follow-up examination data.

12.10 ABSOLUTE BASOPHILS

At the 1992 follow-up examination, absolute basophil counts increased with increasing levels of 1987 dioxin among Black Ranch Hands.

12.11 ABSOLUTE NEUTROPHILS

Absolute neutrophil counts increased among Black Ranch Hand participants and among officers with increasing initial dioxin levels at the 1992 follow-up examination. In addition, the 1992 follow-up examination analysis detected increased absolute neutrophil counts as 1987 dioxin levels increased among Black Ranch Hands.

At the 1997 follow-up examination, Ranch Hands in the low and high dioxin categories combined had a higher average absolute neutrophil count than Comparisons.

12.12 RBC MORPHOLOGY

The 1992 follow-up examination revealed an increase in the occurrence of abnormal RBC morphology results as 1987 dioxin levels increased.

Ranch Hand enlisted groundcrew at the 2002 follow-up examination had a greater prevalence of RBC morphology abnormalities than Comparison enlisted groundcrew. In addition, Ranch Hands in the high dioxin category had a greater occurrence of RBC morphology abnormalities than Comparisons.

12.13 ERYTHROCYTE SEDIMENTATION RATE

Ranch Hands at the 1985 follow-up examination had a greater prevalence of erythrocyte sedimentation rate elevations than Comparisons.

The 1987 follow-up examination analyses found that Ranch Hands in the high dioxin category had a greater average erythrocyte sedimentation rate than Comparisons. This result was observed when all Ranch Hands were examined, as well as when the analysis was restricted to older Ranch Hands and Comparisons. Younger Ranch Hands in the low dioxin category had a greater average erythrocyte sedimentation rate than younger Comparisons. Similarly, Ranch Hands had a greater percentage of erythrocyte sedimentation rate elevations than Comparisons; this pattern also was seen when Ranch Hands were categorized with both low dioxin levels and high dioxin levels. Erythrocyte sedimentation rates and the prevalence of erythrocyte sedimentation rate elevations increased in Ranch Hands as initial dioxin levels increased and as 1987 dioxin levels increased.

Erythrocyte sedimentation rates at the 1992 and 1997 follow-up examinations increased with increasing 1987 dioxin levels. The percentage of erythrocyte sedimentation rate elevations observed at the 1992 follow-up examination increased with increasing 1987 dioxin levels.

Ranch Hands in the low and high dioxin categories combined had a greater average erythrocyte sedimentation rate than Comparisons at the 2002 follow-up examination.

12.14 RELATION OF SERUM 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) LEVEL TO HEMATOLOGICAL EXAMINATION RESULTS IN VETERANS OF OPERATION RANCH HAND

A journal article published in 2001 (8) provided results of a study of indices of hematologic function at the 1982, 1985, 1987, and 1992 AFHS examinations and their relations to dioxin and herbicides. No consistent relations between dioxin and RBC count, hemoglobin, hematocrit, WBC count, and erythrocyte sedimentation rate were found. Mean corpuscular volume and platelet count generally increased with increasing dioxin levels at each of these four AFHS examinations. The elevation in average levels of mean corpuscular volume and platelet count for Ranch Hands in the high dioxin category was minimal, however, and suggested that the findings, if causal, have little clinical significance.

12.15 CONCLUSION

These hematology results point to a relation between platelet count and erythrocyte sedimentation rate and exposure to herbicides and dioxin, but the biologic significance of these findings is uncertain. Increased platelet counts, in addition to the elevated erythrocyte sedimentation rates, may indicate the presence of a chronic inflammatory response to dioxin.

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13 IMMUNOLOGY ASSESSMENT

13.1 INTRODUCTION

Overt damage to organs of the immune system and depressed immunologic function has been noted in a variety of animals exposed to dioxin. As the fields of immunology and immunotoxicology have grown in the past 25 years, a significant spectrum of subtle immunotoxic effects has also been described in animals, but for many possible reasons comparable adverse effects have not been recorded consistently in exposed humans.

Data from the physical examination (skin test measurements at the 1985 and 1987 follow-up examinations, as described below) and the immunology laboratory were used to assess the immunological function for the 1982, 1985, 1987, 1992, 1997, and 2002 Air Force Health Study (AFHS) examinations (1-7).

Absolute lymphocytes indicated the density of lymphocytes in the blood and were analyzed at all six of the AFHS physical examinations. Lymphocytes recognize and destroy bacteria, fungi, viruses, and other foreign bodies.

Responses to stimulation by pokeweed mitogen (PWM) were analyzed for the 1985 follow-up examination. The PWM study measured the functional capability of T cells to become activated by mitogen and undergo proliferations.

Cell function responses to stimulation by phytohemagglutinin (PHA), mixed lymphocyte culture (MLC), and two natural killer cell assays were analyzed for the 1985 and 1987 follow-up examinations. The PHA studies measure the functional capability of T-cells to become activated by mitogen and undergo proliferation. The MLC studies measured the reactivity of T cells to foreign histocompatibility class II antigens. The natural killer cells studies measured natural killer cell activity without Interleukin-2 (NKCA) and with Interleukin-2 (NKCI).

For the 1987 and 1992 follow-up examinations, a composite skin test was constructed based on the responses to four separate antigens – *Candida albicans*, mumps, Trichophyton, and staph-phage lysate. The antigens were injected intradermally and a positive response to any of the four indicated intact cell-mediated immunity. The skin test was considered abnormal if none of the four antigen responses was positive and normal if one or more of the antigen responses was positive.

Immunoglobulins measure the ability of a specific B-cell subgroup to secrete a specific antibody class of molecules. The antibodies typically rise in response to infections or immunizations with bacteria, fungi, and viruses. Analyses were performed on immunoglobulins IgA, IgG, and IgM for 1987, 1992, 1997, and 2002 follow-up examinations.

For the 1992 examination, B cell clones as detected by serum protein electrophoresis and other antibodies were studied, but no associations with group or dioxin were found.

Lupus panel tests were performed for the 1992, 1997, and 2002 follow-up examinations. These tests detected the most frequent autoantibodies found in humans. Autoantibodies are markers for autoimmune diseases, and the lupus panel is considered a screening assay for a wide spectrum of autoimmune

disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus). Occasionally, autoantibodies are detected in asymptomatic persons; this is alternatively explained as evidence for incipient autoimmune disease or a finding of unknown meaning. The lupus panel, based on the manual indirect fluorescent antibody method, comprises the following individual tests on serum that follow:

- Antinuclear antibody (ANA) performed on HEp-2 cells
- Thyroid microsomal antibody
- Mouse stomach kidney (MSK) section stain for the following specific autoantibodies:
 - Anti-smooth muscle
 - Anti-mitochondrial
 - Anti-parietal cell
- Rheumatoid factor.

All the autoantibodies derive from abnormalities of the B-cell portion, the part of the immune system that produces immunoglobulins.

Cell surface marker measurements were carried out on a random sample of approximately 40 percent of the participants because of the complexity of the assay and the expense of the tests. Quantification of the different cell populations was carried out with the use of reagent mouse monoclonal antibodies. CD4+ cells (helper T cells), CD8+ cells (suppressor cells), and CD20+ cells (B cells) were analyzed for all six AFHS examinations. The cell surface marker measurements of CD2+ cells, CD3+ cells, CD5+ cells, CD14+ cells, CD16+56+ cells, CD25+ cells, and human leukocyte antigen-DR (HLA-DR) cells were analyzed at one or more of the AFHS examinations. Analysis of double-labeled cells (cells that express two markers) were done for CD3+ with CD25+, CD5+ with CD20+, CD4+ with CD8+, and CD3- with CD16+56+ at the 1992 follow-up examination, and CD3+CD4+ at the 1997 and 2002 follow-up examinations.

The following journal article on the relation of immune response of AFHS participants at the 1992 follow-up examination to dioxin exposure was written by AFHS staff and their colleagues:

- Serum dioxin and immunologic response in veterans of Operation Ranch Hand (8).

In this article, delayed-type hypersensitivity skin test responses were studied. Lymphocyte measurements, including total lymphocyte counts; T cell (CD3+, CD4+, CD5+, and CD8+), B cell (CD20+), and natural killer cell (CD16+ and CD56+) subsets; and expression of the activation antigen CD25+ on CD3+ T cells, also were analyzed. Concentrations of immunoglobulins IgA, IgG, and IgM; the presence of monoclonal immunoglobulins (M proteins); and a broad range of autoantibodies (rheumatoid factor, ANA, smooth muscle autoantibody, mitochondrial autoantibody, parietal cell autoantibody, and thyroid microsomal autoantibodies) were examined. Overall, the authors found no evidence of a consistent relation between dioxin exposure category and immune system alteration.

In 2002, the Institute of Medicine found that the evidence determining whether an association exists between Agent Orange and other herbicides used in Vietnam and immune suppression or autoimmunity was inadequate or insufficient (9). This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (10).

13.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this stratification based on the participant's tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the immunology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Absolute Lymphocytes	X		X	X	X	X	X
CD14+ Cells (Monocytes)		X	X	X	X		
CD16+56+ Cells (Natural Killer Cells)					X	X	X
CD2+ Cells (Total T Cells)	X	X	X	X			
CD20+ Cells (B Cells)	X	X	X	X	X	X	X
CD25+ Cells (Activation Marker for Lymphocytes)			X	X	X		
CD3+ Cells (Total T Cells)	X				X	X	X
CD4+ Cells (Helper T Cells)	X	X	X	X	X	X	X
CD4+–CD8+ Ratio	X	X	X	X	X		
CD5+ Cells (T-cell Marker)					X		
CD8+ Cells (Suppressor Cells)	X	X	X	X	X	X	X
Composite Skin Test Diagnosis			X	X	X		
Double Labeled Cells: CD3- with CD16+56+					X		
Double Labeled Cells: CD3+ with CD25+					X		
Double Labeled Cells: CD3+CD4+Cells (Helper T Cells)						X	X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Double Labeled Cells: CD4+ with CD8+					X		
Double Labeled Cells: CD5+ with CD20+					X		
HLA-DR Cells		X	X	X			
IgA			X	X	X	X	X
IgG			X	X	X	X	X
IgM			X	X	X	X	X
Lupus Panel: ANA Test					X	X	X
Lupus Panel: ANA Thyroid Microsomal Antibody					X	X	X
Lupus Panel: B-Cell Clones Detected by Serum Protein Electrophoresis					X		
Lupus Panel: MSK Anti-Mitochondrial Antibody					X	X	X
Lupus Panel: MSK Anti-Parietal Antibody					X	X	X
Lupus Panel: MSK Anti-Smooth Muscle Antibody					X	X	X
Lupus Panel: Other Antibodies					X		
Lupus Panel: Rheumatoid Factor					X	X	X
Lupus Panel: Summary Index					X		
MLC: Net Response			X	X			
MLC: Unstimulated Response			X	X			
NKCA 50/1: Net Response			X	X			
NKCA 50/1: Percent Release			X	X			
NKCI 50/1: Net Response			X	X			
NKCI 50/1: Percent Release			X	X			
PHA: Maximum Net Response			X	X			
PHA: Net Response			X	X			
PHA: Unstimulated Response			X	X			

13.2 COMPOSITE SKIN TEST DIAGNOSIS

Analysis of 1987 follow-up examination data showed that among all participants and among the heaviest lifetime cigarette smokers, Ranch Hands had a greater prevalence of composite skin test abnormalities than Comparisons.

Analyses of data from the 1992 follow-up examination found that a greater percentage of Ranch Hands in the background dioxin category than Comparisons had an abnormal composite skin test diagnosis.

13.3 CD2+ CELLS (TOTAL T CELLS)

The 1985 follow-up examination found that Black Ranch Hands had a lower average CD2+ cell count than Black Comparisons.

Among participants who drank more than one drink per day, CD2+ cell counts at the 1987 follow-up examination decreased with increasing levels of initial dioxin. In addition, younger Ranch Hands in the

background dioxin category who were moderate lifetime drinkers (no more than 40 drink-years) had a lower average CD2+ cell count than younger Comparisons who were moderate lifetime drinkers.

13.4 CD3+ CELLS (TOTAL T CELLS)

Among officers at the 1992 follow-up examination, Ranch Hands in the high dioxin category had a greater average CD3+ cell count than Comparisons.

Analysis of data collected for the 1997 follow-up examination showed that CD3+ cell counts in Ranch Hands increased with increasing 1987 dioxin levels.

13.5 CD4+ CELLS (HELPER T CELLS)

Among Ranch Hands who were moderate lifetime drinkers (no more than 40 drink-years) with later tours of duty who participated in the 1987 follow-up examination, CD4+ cell counts decreased as 1987 dioxin levels increased.

Analysis of CD4+ cells for the 1992 follow-up examination found that Ranch Hand officers in the high dioxin category had a greater average CD4+ cell count than Comparison officers.

CD4+ cell counts in Ranch Hands at the 1997 follow-up examination increased with increasing 1987 dioxin levels.

13.6 CD5+ CELLS (T-CELL MARKER)

Analysis of CD5+ cells for the 1992 follow-up examination showed Ranch Hand officers in the high dioxin category had a greater average CD5+ cell count than Comparison officers.

13.7 CD8+ CELLS (SUPPRESSOR CELLS)

Among the heaviest drinkers (current and lifetime) as of the 1987 follow-up examination, CD8+ cell counts decreased with increasing levels of initial dioxin.

Among officers, CD8+ cell counts increased at the 1992 follow-up examination with initial dioxin levels. In addition, the categorized dioxin analysis showed that among officers, Ranch Hands in the high dioxin category had a greater average CD8+ cell count than Comparisons. Ranch Hand enlisted flyers in the high dioxin category had a lower mean CD8+ cell count than Comparison enlisted flyers. Ranch Hand enlisted groundcrew in the background dioxin category had a greater average CD8+ cell count than Comparison enlisted groundcrew.

13.8 CD4+—CD8+ RATIO

The 1992 follow-up examination analysis of the ratio of CD4+ cells to CD8+ cells found that among participants with moderate physical activity, Ranch Hands had a greater average ratio than Comparisons.

13.9 CD14+ CELLS (MONOCYTES)

Analysis of CD14+ cells at the 1985 follow-up examination showed that among enlisted groundcrew who were currently drinking the most (more than four drinks per day), Ranch Hands had a greater average CD14+ cell count than Comparisons.

Among the heaviest lifetime smokers at the time of the 1987 follow-up examination (more than 10 pack-years) with earlier tours of duty, CD14+ cell counts increased with increasing 1987 dioxin levels.

The 1992 follow-up examination analysis of CD14+ cells found Ranch Hand enlisted flyers had a lower average CD14+ cell count than Comparison enlisted flyers. In addition, older Ranch Hands in the low dioxin category had lower average CD14+ cell counts than older Comparisons.

13.10 CD16+56+ CELLS (NATURAL KILLER CELLS)

At the 1987 follow-up examination, Ranch Hand officers showed an increase in CD16+56+ counts with increasing initial dioxin levels. In addition, among officers and lifetime nondrinkers, Ranch Hands in the high dioxin category had a greater average CD16+56+ cell count than Comparisons. A lower average CD16+56+ cell count was seen among Ranch Hands in the low dioxin category who were moderate drinkers (no more than 40 drink-years) or who were moderately active than among Comparisons. Ranch Hand enlisted flyers in the high dioxin category and Ranch Hand officers in the low dioxin category had lower average CD16+56+ cell counts than Comparison enlisted flyers and Comparison officers, respectively.

Among enlisted flyers at the 1997 follow-up examination, Ranch Hands had a lower average CD16+56+ cell count than Comparisons. Similarly, Ranch Hands in the high dioxin category had a lower average CD16+56+ cell count than Comparisons.

13.11 CD20+ CELLS (B CELLS)

The 1985 follow-up examination of CD20+ cells revealed that among Non-Black participants who never smoked, Ranch Hands had a lower average CD20+ cell count than Comparisons.

Among older Ranch Hands who participated in the 1987 follow-up examination, CD20+ cell counts increased as initial dioxin levels increased. Also, among older participants, Ranch Hands in the background dioxin category, as well as Ranch Hands in the high dioxin category, had greater average CD20+ cell counts than Comparisons. Analysis of 1987 follow-up examination data also showed that among Ranch Hands with earlier tours of duty, CD20+ cell counts increased with increasing 1987 dioxin levels.

The analysis of CD20+ cells at the 1992 follow-up examination found that Ranch Hands in the background dioxin category had greater average CD20+ cell counts than Comparisons.

An increase in CD20+ cells counts in Ranch Hands was seen at the 2002 follow-up examination as initial dioxin levels increased.

13.12 CD25+ CELLS (ACTIVATION MARKER FOR LYMPHOCYTES)

Among Ranch Hands who were current cigarette smokers, lighter lifetime smokers and drinkers, and participated in the 1987 follow-up examination, CD25+ cell counts increased with increasing initial dioxin levels. CD25+ cell counts decreased with increasing 1987 dioxin levels for Ranch Hands with later tours of duty.

The analysis of CD25+ cells at the 1992 follow-up examination showed that among enlisted flyers, Ranch Hands had a lower average CD25+ cell count than Comparisons. Ranch Hand enlisted flyers in the low and high dioxin categories combined also had a lower average CD25+ cell count than Comparison enlisted flyer. Ranch Hand officers in the high dioxin category had a greater average CD25+ cell count than Comparison officers. In addition, among participants who did not drink, Ranch Hands in the high dioxin category had greater average CD25+ cell counts than Comparisons.

13.13 HUMAN LEUKOCYTE ANTIGEN (HLA)-DR CELLS

Among younger Ranch Hands who participated in the 1987 follow-up examination, HLA-DR counts decreased as initial dioxin levels increased. Among older participants, and, in particular, among older participants who currently drank no more than one drink per day, HLA-DR counts increased with increasing initial dioxin levels. In addition, among older participants, Ranch Hands in the high dioxin category had a greater average HLA-DR count than Comparisons.

13.14 DOUBLE-LABELED CELLS

13.14.1 CD3- with CD16+56+

Analysis for the 1992 follow-up examination found that the number of cells that expressed both CD3- and CD16+56+ markers decreased with increasing 1987 dioxin levels.

13.14.2 CD3+ with CD25+

Among enlisted flyers at the 1992 follow-up examination, Ranch Hands (in particular, Ranch Hands in the low and high dioxin categories combined) had a lower average CD3+ with CD25+ cell count than Comparisons. Among lifetime nondrinkers and among officers, Ranch Hands who were in the high dioxin category had a higher average CD3+ with CD25+ cell count than Comparisons.

13.14.3 CD4+ with CD8+

Among Blacks and officers at the 1992 follow-up examination, Ranch Hands in the background dioxin category had a lower average CD4+ with CD8+ cell count than their Comparison counterparts. In addition, older Ranch Hands in the low dioxin category had a lower average CD4+ with CD8+ cell count than older Comparisons. Ranch Hand enlisted groundcrew in the background dioxin category had a higher average CD4+ with CD8+ cell count than Comparison enlisted groundcrew.

13.14.4 CD5+ with CD20+

Analysis of 1992 follow-up examination data showed that the number of cells that express both CD5+ and CD20+ markers increased with increasing 1987 dioxin levels.

211 **13.14.5 CD3+CD4+ Cells (Helper T Cells)**

212 The analysis for the 1997 follow-up examination revealed an increase in CD3+CD4+ cell counts in Ranch
213 Hands as 1987 dioxin levels increased.

214 **13.15 ABSOLUTE LYMPHOCYTES**

215 Among Ranch Hands who drank more than one drink per day and participated in the 1987 follow-up
216 examination, absolute lymphocytes decreased as initial dioxin levels increased. Among younger
217 participants who were moderate lifetime drinkers (less than 40 drink-years at the time of the
218 examination), Ranch Hands in the background dioxin category had a lower average absolute lymphocyte
219 count than Comparisons. In addition, younger Ranch Hands in the high dioxin category who were
220 lifetime nondrinkers had a lower average absolute lymphocyte count than their Comparison counterparts.

221 The 1992 follow-up examination found that among moderately active Ranch Hands, absolute
222 lymphocytes increased with increasing initial dioxin levels.

223 **13.16 MAXIMUM PHYTOHEMAGGLUTININ (PHA) NET RESPONSE**

224 The 1987 follow-up examination analysis found that Ranch Hands with later tours of duty had increased
225 maximum PHA net response values as 1987 dioxin levels increased.

226 **13.17 PHA NET RESPONSE**

227 Among heavy drinkers who participated in the 1987 follow-up examination, Ranch Hands had a lower
228 average PHA net response value than Comparisons. Ranch Hands in the background dioxin category
229 who were heavy drinkers had a greater average PHA net response than their Comparison counterparts.
230 PHA net response values among Ranch Hands who were the heaviest lifetime drinkers with later tours of
231 duty increased with increasing 1987 dioxin levels. PHA net response values increased with increasing
232 initial dioxin among the heaviest lifetime drinkers and decreased with increasing initial dioxin among
233 nondrinkers.

234 **13.18 UNSTIMULATED MIXED LYMPHOCYTE CULTURE (MLC) RESPONSE**

235 Analysis of data from the 1987 follow-up examination showed that Ranch Hands in the high dioxin
236 category had a greater average unstimulated MLC response than Comparisons. In addition, among Ranch
237 Hands who were lifetime nonsmokers and had earlier tours of duty, unstimulated MLC values increased
238 as 1987 dioxin levels increased.

239 **13.19 NATURAL KILLER CELL ASSAY (NKCA) 50/1 PERCENT RELEASE**

240 Analysis of data from the 1987 follow-up examination found that Black Ranch Hands had a greater
241 average NKCA 50/1 percent release than Black Comparisons.

13.20 NATURAL KILLER CELL ASSAY WITH INTERLEUKIN-2 (NKCI) 50/1 PERCENT RELEASE AND NET RESPONSE

Black Ranch Hands in the 1987 follow-up examination had a greater average NKCI percent release than Black Comparisons. Among non-Black participants who were the heaviest drinkers, Ranch Hands in the low dioxin category had a greater average NKCI percent release than Comparisons. In addition, among non-Black participants with later tours of duty and among Black participants with earlier tours of duty, NKCI percent release values increased with increasing levels of 1987 dioxin.

The same results were seen for NKCI 50/1 net response at the 1987 follow-up examination.

13.21 IgA

Among Ranch Hands with earlier tours of duty who used to smoke but quit and participated in the 1987 follow-up examination, IgA values increased with increasing 1987 dioxin levels. Ranch Hands in the background dioxin category had a lower average IgA value than Comparisons.

IgA values in Ranch Hands at both the 1987 and 1997 follow-up examinations increased with increasing initial dioxin levels.

Among Black participants at the 1992 follow-up examination, Ranch Hands in the low dioxin category had a greater average IgA value than Comparisons.

13.22 IgG

At the 1987 follow-up examination, Ranch Hands in the background dioxin category had a lower average IgG value than Comparisons. At the 1992 follow-up examination, Ranch Hand officers in the high dioxin category had a lower average IgG value than Comparison officers.

13.23 IgM

Among Ranch Hands who were moderate current drinkers (between one and four drinks per day) and participated in the 1987 follow-up examination, IgM values decreased with increasing initial dioxin levels. Analysis for the 1987 follow-up examination also found that, among Ranch Hands with later tours of duty, IgM values decreased with increasing 1987 dioxin levels.

Based on data from the 1992 follow-up examination, Black Ranch Hands had a lower average IgM value than Black Comparisons. Similarly, among sedentary participants (in particular, sedentary enlisted flyers), Ranch Hands had a lower average IgM value than their Comparison counterparts. Very active Ranch Hands (primarily in the low dioxin category), however, had a greater average IgM value than Comparisons.

Ranch Hand enlisted flyers at the 2002 follow-up examination had a lower average IgM value than Comparison enlisted flyers.

13.24 LUPUS PANEL

13.24.1 Antinuclear Antibody (ANA) Test

At the 2002 follow-up examination, the presence of ANA increased with increasing initial dioxin levels.

13.24.2 ANA Thyroid Microsomal Antibody

Among heaviest lifetime drinkers (more than 40 drink-years at the time of the examination) and among all minimal current drinkers (no more than one drink per day), a greater percentage of Ranch Hands than Comparisons had thyroid microsomal antibodies present at the 1992 follow-up examination.

Among participants who were currently smoking cigarettes at the time of the 1992 follow-up examination, a greater percentage of Ranch Hands in each of the background, low, and high dioxin categories than Comparisons had thyroid microsomal antibodies present. Among former smokers and the heaviest lifetime drinkers, Ranch Hands in the low dioxin category and in the high dioxin category each had a greater prevalence of thyroid microsomal antibodies present than Comparisons. Among minimal current drinkers, a greater percentage of Ranch Hands in the low dioxin category than Comparisons had thyroid microsomal antibodies present.

13.24.3 Mouse Stomach Kidney (MSK) Anti-smooth Muscle Antibody

The 2002 follow-up examination found that Ranch Hand officers had a greater presence of anti-smooth muscle antibodies than Comparison officers. In addition, a greater percentage of Ranch Hands in the background dioxin category had anti-smooth muscle antibodies present than Comparisons.

13.24.4 Rheumatoid Factor

Among Ranch Hand enlisted groundcrew who participated in the 1992 follow-up examination, the occurrence of a positive rheumatoid factor increased with initial dioxin levels. In addition, among Ranch Hands in the background dioxin category, enlisted groundcrew and moderately physically active participants had a greater presence of positive rheumatoid factor results than their Comparison counterparts.

A greater percentage of Ranch Hand officers at the 2002 follow-up examination had a positive rheumatoid factor than Comparison officers. In addition, Ranch Hands in the low dioxin category had a higher prevalence of positive rheumatoid factor results than Comparisons.

13.25 CONCLUSION

Consistent with previous AFHS physical examinations, IgA increased with increasing initial dioxin at the 1997 follow-up examination, but was not increased in enlisted groundcrew or the high dioxin category. The IgA results were small in magnitude and their clinical significance was unknown.

In the lupus panel, a positive association was found between initial dioxin level and the presence of the ANA at the 2002 follow-up examination, but the association did not appear to support a dose-response relation. There was an increasing prevalence of a positive ANA in Ranch Hands with increasing initial dioxin levels. When looking at the individual autoantibodies, however, there were no consistent findings to support the presence of ANA.

310 The indices of immune responses analyzed in the AFHS examination provided a comprehensive
311 reflection of in vivo and in vitro immune function in the study population. No biologically meaningful
312 indicators reflecting a relation between the body burden of dioxin or the initial exposure and immune
313 function were found.

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14 NEOPLASIA ASSESSMENT

14.1 INTRODUCTION

Many types of cancer are thought to be related to chlorophenols, phenoxy herbicides, and dioxin. Although exposure to herbicides has been determined to be carcinogenic in animal studies, the exposure required for malignant transformation of normal cells and the types of tumors produced are species-dependent. Therefore, while animal studies provide conclusive evidence on the carcinogenic potential of dioxin, the determination of causality in humans remains to be established.

Many studies have assessed the carcinogenic potential of dioxin in humans. While the cumulative data from these studies have not been entirely consistent, associations between dioxin exposure in humans and an increased risk of developing cancers of the skin, lung, bladder, kidney, connective tissue, and lymphatic system have been reported.

During the health interview at the 1982, 1985, 1987, 1992, 1997, and 2002 Air Force Health Study (AFHS) examinations, each study participant was asked a series of questions on the occurrence of cancer. Medical records review was accomplished to confirm reported neoplasms and identify any unreported neoplasms. The data were combined to form a complete lifetime neoplasia history for each participant. These data were the basis of the majority of the analysis for the neoplasia assessment (1-7). The neoplasia assessment itself was based on the occurrence of neoplasms (both benign and malignant) after service in Southeast Asia (SEA).

Some possible neoplasms were discovered by the physicians at the physical examination. Contingent upon participant authorization, suspicious skin lesions were biopsied and the pathology determined; no other invasive procedures were used to detect systemic neoplasms.

For chest x-ray findings needing follow-up at the 2002 physical examination, the AFHS staff made every effort to contact and encourage participants to see their primary physicians. The participants were then recontacted to determine whether a final diagnosis was available, and, if so, results were included in the analysis.

In the AFHS examination reports, skin neoplasms were analyzed by behavior. In particular, analysis was conducted on skin neoplasms according to the following four behaviors:

- All skin neoplasms
- Malignant skin neoplasms
- Benign skin neoplasms
- Skin neoplasms of uncertain behavior or unspecified nature.

Analysis of malignant skin neoplasms was conducted for all sites combined and by the following cell types:

- Basal cell carcinoma

- Squamous cell carcinoma
- Sun exposure-related neoplasm (basal cell carcinoma, squamous cell carcinoma, melanoma, and malignant epithelial neoplasms not otherwise specified)
- Nonmelanoma (basal cell carcinoma, squamous cell carcinoma, and malignant epithelial neoplasms not otherwise specified)
- Melanoma.

Systemic neoplasms were analyzed by behavior. In particular, analysis was conducted on systemic neoplasms according to the following four behaviors:

- All systemic neoplasms
- Malignant systemic neoplasms
- Benign systemic neoplasms
- Systemic neoplasms of uncertain behavior or unspecified nature.

Analysis of malignant systemic neoplasms also was conducted based on the site of the neoplasms. The various sites examined are described later in this chapter.

In addition, analysis was performed on all skin and systemic neoplasms, regardless of behavior or site, and all malignant neoplasms, which was a combination of malignant skin and malignant systemic neoplasms.

The prostate-specific antigen (PSA) test was developed to detect prostate enlargement and prostate cancer. Each participant had a PSA test as a standard part of the laboratory assay.

The following journal articles on skin and systemic cancer were written by AFHS staff and their colleagues:

- Serum dioxin and cancer in veterans of Operation Ranch Hand (8)
- Cancer in US Air Force veterans of the Vietnam War (9)
- Did TCDD exposure or service in Southeast Asia increase the risk of cancer in Air Force Vietnam veterans who did not spray Agent Orange? (10).

The Institute of Medicine (IOM), as reported first in their 1994 publication, *Veterans and Agent Orange* (11), concluded that there is “sufficient” evidence to establish an association, although not a causal relation, between dioxin exposure and the occurrence of soft tissue sarcoma, non-Hodgkin’s lymphoma, and Hodgkin’s disease (11-16). In the 2002 *Veterans and Agent Orange* update, the epidemiologic evidence was considered to be sufficient concerning chronic lymphocytic leukemia based primarily on studies of agricultural workers (15). The evidence for an association with respiratory cancers, prostate cancer, and multiple myeloma was considered “limited/suggestive” (11-16).

14.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this stratification based on the participant's tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the neoplasia assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
<i>Skin Neoplasms</i>							
All		X	X	X	X	X	X
Malignant		X	X	X	X	X	X
Basal Cell Carcinoma	X	X	X	X	X	X	X
Fibrosarcoma	X						
Melanoma	X	X	X	X	X	X	X
Nonmelanoma					X	X	X
Squamous Cell Carcinoma	X	X	X	X	X	X	X
Sun Exposure-Related		X	X	X			
Benign		X	X	X	X	X	X
Uncertain Behavior or Unspecified Nature		X	X	X	X	X	X
<i>Systemic Neoplasms</i>							
All		X	X	X	X	X	X
All Stomach							X
Malignant		X	X	X	X	X	X
Bone and Articular Cartilage	X						X
Brain			X	X	X	X	X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Bronchus and Lung	X	X	X	X	X	X	X
Carcinoma In Situ (Breast, Digestive Organs, Respiratory, Prostate, Penis and Other Male Genitals, and Bladder and Other and Nonspecified Urinary)			X	X	X	X	X
Colon and Rectum		X	X	X	X	X	X
Connective and Other Soft Tissues		X			X	X	X
Digestive Organ, Peritoneum, and Esophagus	X	X			X	X	X
Eye, Ear, Face, Head, and Neck		X	X	X	X	X	X
Hodgkin's Disease	X	X	X	X	X	X	X
Ill-Defined Sites		X	X	X	X	X	X
Urinary System		X	X	X	X	X	X
Kidney and Ureter							X
Leukemia		X	X	X	X		X
Lip, Oral Cavity, Pharynx, and Larynx	X	X	X	X	X	X	X
Liver						X	X
Lymphoreticular Sarcoma							X
Multiple Myeloma					X		X
Non-Hodgkin's Lymphoma		X			X	X	X
Other Malignant Systemic Neoplasms of Lymphoid and Histiocytic Tissue	X		X	X	X	X	X
Penis and Other Male Genital Organs	X						X
Prostate		X	X	X	X	X	X
Soft Tissue Sarcoma		X					
Stomach							X
Testicles		X	X	X	X	X	X
Thymus, Heart, and Mediastinum			X	X	X	X	X
Thyroid Gland		X	X	X	X	X	X
Benign		X	X	X	X	X	X
Uncertain Behavior or Unspecified Nature		X	X	X	X	X	X
<i>Skin and Systemic Neoplasms</i>							
All		X	X	X	X	X	X
Malignant						X	X
<u>PSA</u>					X	X	X

92

93 14.2 SKIN NEOPLASMS

94 14.2.1 All Skin Neoplasms

95 When the 1992 follow-up examination data were analyzed, the prevalence of any type of skin neoplasm
96 was higher for Ranch Hands in the low dioxin category than Comparisons.

In the analysis of the 1997 follow-up examination data, the prevalence of any type of skin neoplasm was higher in Ranch Hands than Comparisons among all participants, among officers, and among enlisted flyers. Ranch Hands in the background and low dioxin categories also had a higher prevalence of any type of skin neoplasm than Comparisons.

The analysis of the 2002 follow-up examination data showed that among all participants, Ranch Hands had a higher prevalence of any type of skin neoplasm than Comparisons. Ranch Hands in the low dioxin category also had a higher prevalence of any type of skin neoplasm than Comparisons.

14.2.2 Malignant Skin Neoplasms

The analysis of the 1982 baseline examination data showed that Ranch Hands had a higher prevalence of a malignant skin neoplasm than Comparisons.

The 1992 follow-up examination data analysis showed that, among participants who did not report exposure to industrial chemicals, Ranch Hands in the low dioxin category had a higher prevalence of a malignant skin neoplasm than Comparisons.

A higher percentage of Ranch Hands in the low dioxin category than Comparisons had a malignant skin neoplasm in the 2002 follow-up examination data analysis.

14.2.2.1 Basal Cell Carcinoma

In 1985, the analysis of the follow-up examination data showed a higher prevalence of basal cell carcinoma among Ranch Hand enlisted flyers than Comparison enlisted flyers.

The analysis of the 1987 follow-up examination data showed a higher percentage of Ranch Hands with basal cell carcinoma than Comparisons.

Data from the 1987 follow-up examination also showed that Ranch Hands in the background and low dioxin categories had a higher prevalence of basal cell carcinoma at multiple sites than Comparisons. The prevalence of basal cell carcinoma on sites that were not specified increased with increasing initial dioxin among Ranch Hand enlisted flyers. In addition, Ranch Hands in the low dioxin category had a higher prevalence than Comparisons of basal cell carcinoma on sites that were not specified. Among enlisted flyers, however, Ranch Hands in the high dioxin category had a higher prevalence of basal cell carcinoma on sites that were not specified than Comparisons.

The analysis of the 1992 follow-up examination data showed that the prevalence of basal cell carcinoma on the trunk increased with increasing 1987 dioxin levels among Ranch Hand participants who did not report exposure to insecticides (a covariate in the analysis).

The 1997 follow-up examination data analysis showed a higher prevalence of basal cell carcinoma in Ranch Hand enlisted flyers than Comparison enlisted flyers. In addition, Ranch Hands in the low dioxin category had a higher prevalence of basal cell carcinoma than Comparisons. The prevalence of basal cell carcinoma on the trunk for Ranch Hands also increased with increasing 1987 dioxin levels.

The 2002 follow-up examination data analysis showed that among all participants and among officers, Ranch Hands had a higher prevalence of basal cell carcinoma than Comparisons. Ranch Hands in the low dioxin category also had a higher prevalence of basal cell carcinoma than Comparisons.

14.2.2.2 *Nonmelanoma*

The 1997 follow-up examination data analysis showed that Ranch Hand enlisted flyers had a higher prevalence of a nonmelanoma malignant skin neoplasm than Comparison enlisted flyers.

Ranch Hands had a higher prevalence of a nonmelanoma malignant skin neoplasm than Comparisons in the analysis of the 2002 follow-up examination data; this difference was seen primarily in officers. In addition, a greater percentage of Ranch Hands in the low dioxin category had a nonmelanoma malignant skin neoplasm than Comparisons.

14.2.2.3 *Sun Exposure-related Malignant Skin Neoplasm*

The analysis of the 1987 follow-up examination data showed that Ranch Hands had a higher prevalence of a sun exposure-related malignant skin neoplasm than Comparisons. Ranch Hands in the low dioxin category had a higher prevalence of a sun exposure-related malignant skin neoplasm than Comparisons on sites that were not specified. Among enlisted flyers, Ranch Hands in the high dioxin category also had a greater prevalence of a sun exposure-related malignant skin neoplasm than Comparisons on sites that were not specified. In addition, the prevalence of Ranch Hand enlisted flyers with a sun exposure-related malignant skin neoplasm on sites that were not specified increased with increasing initial dioxin.

14.2.2 **Benign Skin Neoplasms**

The analysis of the 1997 follow-up examination data showed that the prevalence of a benign skin neoplasm was higher in Ranch Hands than in Comparisons among officers. Ranch Hands in the background dioxin category also had a greater prevalence of a benign skin neoplasm than Comparisons.

14.2.3 **Skin Neoplasms of Uncertain Behavior or Unspecified Nature**

The 2002 follow-up examination data analysis showed that the prevalence of a skin neoplasm of uncertain behavior or unspecified nature was greater for Ranch Hands in the low dioxin category than for Comparisons.

14.3 **SYSTEMIC NEOPLASMS**

Statistical power is an issue in a study with a population the size of the AFHS. A study with a population of the approximately 2,000 veterans who completed physical examinations lacks power to determine increases in relative risks for rare events (such as soft tissue sarcoma and other systemic neoplasms) because such events are unlikely to occur in large numbers in a group this small. While certain occupational toxins have a clear diagnostic pathology (e.g., mesothelioma for asbestos, hepatic angiosarcoma for vinyl chloride) that is virtually nonexistent in the absence of the causative agent, other toxins merely increase the risk of nondiagnostic pathology. For example, the AFHS would likely not discern an increase in the relative risk for a rare tumor that does not have a clear diagnostic pathology.

14.3.1 **All Systemic Neoplasms**

The 1987 follow-up examination data analysis showed that the prevalence of any type of systemic neoplasm in Ranch Hands increased with increasing initial dioxin. The prevalence of any type of systemic neoplasm in Ranch Hands with later tours also increased with increasing 1987 dioxin.

14.3.2 Malignant Systemic Neoplasms

The 1985 follow-up examination data analysis showed that Ranch Hand enlisted flyers had a higher prevalence of a malignant systemic neoplasm than Comparison enlisted flyers.

Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm than Comparisons in the analysis of the 1987 follow-up examination data.

The analysis of the 1992 follow-up examination data showed that the prevalence of a malignant systemic neoplasm increased with increasing 1987 dioxin levels among Ranch Hands who did not report exposure to degreasing chemicals.

Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm than Comparisons in the analysis of the 1997 follow-up examination data.

The 2002 follow-up examination data analysis showed Ranch Hand officers had a higher prevalence of a malignant systemic neoplasm than Comparison officers. In addition, a higher percentage of Ranch Hands in the low dioxin category had a malignant systemic neoplasm than Comparisons.

14.3.2.1 *Bronchus and Lung*

The analyses of the 1997 and 2002 follow-up examination data showed that Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the bronchus and lung than Comparisons.

14.3.2.2 *Colon and Rectum*

The 1992 and 2002 follow-up examination data analyses showed that the prevalence of a malignant systemic neoplasm of the colon and rectum was higher among Ranch Hands in the low dioxin category than among Comparisons. The analysis of the 2002 follow-up examination data also showed that the prevalence of a malignant systemic neoplasm of the colon and rectum was higher for Ranch Hand officers than Comparison officers.

14.3.2.3 *Eye, Ear, Face, Head, and Neck*

The 1992 follow-up examination data analysis showed that Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the eye, ear, face, head, or neck than Comparisons among moderate lifetime cigarette smokers (more than 0 pack-years but no more than 10 pack-years) and among participants who did not report exposure to degreasing chemicals.

14.3.2.4 *Liver*

The analysis of the 1997 follow-up examination data showed that the prevalence of a malignant systemic neoplasm of the liver among Ranch Hands increased with increasing 1987 dioxin levels.

14.3.2.5 *Malignant Systemic Neoplasms of the Penis and Other Male Genital Organs*

The 2002 follow-up examination data analysis showed that the prevalence of a malignant systemic neoplasm of the penis and other male genital organs increased with increasing 1987 dioxin levels.

14.3.2.6 Prostate

When the 1992 follow-up examination data were analyzed, the findings showed that the prevalence of a malignant systemic neoplasm of the prostate increased with increasing 1987 dioxin levels among Ranch Hand participants who did not report exposure to degreasing chemicals.

The 2002 follow-up examination data analysis showed that Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the prostate than Comparisons.

14.3.2.7 Urinary System

The analyses of 1987 and 1997 follow-up examination data showed that Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the urinary system than Comparisons.

The analysis of the 2002 follow-up examination data showed that Ranch Hands had a higher prevalence of a malignant systemic neoplasm of the urinary system than Comparisons, primarily among officers. The prevalence of a malignant systemic neoplasm of the urinary system among Ranch Hands increased with increasing initial dioxin. In addition, Ranch Hands in the low dioxin category had a higher prevalence of a malignant systemic neoplasm of the urinary system than Comparisons.

14.3.2.8 Carcinoma in Situ (Breast, Digestive Organs, Respiratory, Prostate, Penis and Other Male Genitals, and Bladder and Other and Nonspecified Urinary)

The analysis of the 2002 follow-up examination data showed that a higher percentage of Ranch Hands in the low dioxin category had a carcinoma in situ than Comparisons.

14.3.3 Benign Systemic Neoplasms

The prevalence of a benign systemic neoplasm in Ranch Hands increased with increasing initial and 1987 dioxin levels in the analysis of the 1997 follow-up examination data.

14.3.4 Systemic Neoplasms of Uncertain Behavior or Unspecified Nature

The analysis of the 1992 follow-up examination data showed that the prevalence of a systemic neoplasm of uncertain behavior or unspecified nature increased with increasing 1987 dioxin among Ranch Hands who reported exposure to asbestos.

14.4 SKIN AND SYSTEMIC NEOPLASMS

14.4.1 All Skin and Systemic Neoplasms

The analysis of the 1992 follow-up examination data showed that the prevalence of any type of skin or systemic neoplasm increased with increasing 1987 dioxin levels among Ranch Hand participants with hazel or green eyes.

In the analysis of the 2002 follow-up examination data, a higher percentage of Ranch Hands in the low dioxin category had an occurrence of any type of skin or systemic neoplasm than Comparisons.

237 **14.4.2 Malignant Skin and Systemic Neoplasms**

238 Both the 1997 and the 2002 follow-up examination data analyses showed that Ranch Hands in the low
239 dioxin category had a higher prevalence of a malignant skin or systemic neoplasm than Comparisons.

240 **14.5 PROSTATE-SPECIFIC ANTIGEN (PSA)**

241 The analysis of the 1992 follow-up examination data showed that the prevalence of abnormally high PSA
242 levels increased with increasing 1987 dioxin among Ranch Hand participants who did not report exposure
243 to degreasing chemicals.

244 **14.6 AFHS JOURNAL ARTICLES ON CANCER**

245 **14.6.1 Serum Dioxin and Cancer in Veterans of Operation Ranch Hand**

246 A 1999 *American Journal of Epidemiology* article (8) described results of an analysis of cancers for all
247 AFHS veterans who attended at least one of the 1982, 1985, 1987, or 1992 examinations and who had a
248 dioxin measurement. All cancers verified as of July 1997 were included. Analysis of cancer prevalence
249 and latency analyses were conducted for all cancers, skin cancers, and cancer at all sites other than the
250 skin. Subgroups of skin cancers and cancer at all sites other than the skin were also analyzed. An
251 inherent limitation of the AFHS is that low statistical power existed to detect an effect for specific or rare
252 cancers.

253 There was no evidence of dose-response pattern or of latency effect for all cancers or for skin cancers.
254 The risk of cancer at sites other than the skin was not increased for Ranch Hands in the high dioxin
255 category, but an increased risk for Ranch Hands in the low dioxin category who had ended their service in
256 SEA within the past 20 years was observed. Kidney or bladder cancer was increased for Ranch Hands in
257 the low dioxin category. Ranch Hands in the low dioxin category, but not in the high dioxin category,
258 had an earlier time to onset of cancer of any type. These results were inconsistent with a NIOSH study of
259 workers at 12 plants in the United States that produced chemicals contaminated with dioxin (17) and
260 suggest that the increased risk may not have been caused by dioxin exposure. Overall, there was no
261 consistent evidence of a dose-response relation and no significant increase in cancer risk in the high
262 dioxin category, the subgroup of greatest interest based on average dioxin levels.

263 **14.6.2 Cancer in US Air Force Veterans of the Vietnam War**

264 An analysis of cancers for all AFHS veterans who attended at least one of the 1982, 1985, 1987, 1992, or
265 1997 examinations was conducted and the results were reported in a 2004 journal article (9). The effects
266 of time spent in SEA, the calendar period of service, and the percentage of SEA service spent in Vietnam
267 were explored relative to cancer in AFHS participants. The conditions included cancers verified as of
268 December 1999. Cancer morbidity was classified by anatomical site using the Surveillance,
269 Epidemiology, and End Results (SEER) section of the National Cancer Institute (NCI) classification
270 system. The SEER categories included all anatomical sites except basal cell and squamous cell
271 carcinoma. Cancer incidence and mortality were considered separately. External contrasts against U.S.
272 national cancer rates and internal analyses by dioxin category were conducted. To maximize available
273 data, all AFHS veterans who attended at least one of the 1982, 1985, 1987, 1992, or 1997 examinations
274 were used for external analysis, whereas the internal measurements used the subset of the participants
275 from the external analyses who additionally had a dioxin measurement.

External contrasts found that the incidences of melanoma and prostate cancer were increased among white Ranch Hand veterans; the same pattern was found when the analysis was restricted to white Ranch Hand participants whose tour of duty occurred between 1966 and 1970, the period of heaviest Agent Orange spraying. The incidence of prostate cancer also was increased among white Comparison veterans; the same pattern was found when the analysis was restricted to Comparison participants whose tour of duty occurred between 1966 and 1970. No significant increases in cancer mortality were found relative to national rates.

Two internal analyses were conducted to address concerns that Comparisons who spent time in Vietnam may have developed cancer. The first analysis was restricted to participants who spent at most 2 years in SEA and the second analysis to Ranch Hands who spent 100 percent of their SEA tours in Vietnam and to Comparisons who spent 0 percent of their SEA tours in Vietnam. Categorization by time spent in SEA approximated categorization by the percentage of SEA service spent in Vietnam. Stratification by the percentage of SEA service spent in Vietnam provided a clearer dichotomy on the Vietnam experience at the expense of a reduction in sample size. Among veterans who spent at most 2 years in SEA, the risk of cancer at any site, of prostate cancer, and of melanoma was increased in the high dioxin category. Among Ranch Hands who spent 100 percent of their SEA tours of duty in Vietnam, the risk of cancer at any site was increased in the low and high dioxin categories relative to Comparisons who spent 0 percent of their SEA tours of duty in Vietnam.

14.6.3 Did TCDD Exposure or Service in Southeast Asia Increase the Risk of Cancer in Air Force Vietnam Veterans Who Did Not Spray Agent Orange?

The effects of time spent in SEA and dioxin level were explored relative to cancer in AFHS Comparison participants and reported in a 2005 journal article by Pavuk et al. (10). Cancer morbidity was classified by anatomical site using the SEER classifications. The SEER categories included all anatomical sites except basal cell and squamous cell carcinoma. The analysis was based on Comparisons who had a dioxin measurement and attended at least one of the six AFHS examinations in 1982, 1985, 1987, 1992, 1997, and 2002. An increased risk of all-sites cancer and trends of increased risks of all SEER sites cancer and melanoma with dioxin were found in AFHS Comparison participants. These veterans had background dioxin levels and were not occupationally exposed to Agent Orange or other herbicides. The results suggested that dioxin acts as an initiator or a promoter of carcinogenesis at low levels or may be a surrogate for other unmeasured risk factors associated with an increased risk of cancer. The results indicated an interrelationship between all-sites cancer, dioxin, and service in SEA, and further suggested that a combination of factors related to time spent in SEA were probably involved. Service in SEA was itself a risk factor for prostate cancer in these AFHS Comparison participants, independent of dioxin exposure. The authors of the journal article noted that interpretation of these results should be made cautiously, as sample sizes for most individual cancer sites were small and detailed locations of individual tours of duty in SEA were not yet available.

14.7 CONCLUSION

The associations between herbicide exposure or dioxin levels and the likelihood of developing cancer were seen primarily for Ranch Hand officers and Ranch Hands in the low dioxin category. No associations were observed for enlisted groundcrew, the military occupational category that had the highest median level of exposure to dioxin in Ranch Hands. Other risk and operational factors discussed in published articles did not show consistent associations in Ranch Hands but did show some associations in the Comparisons. The AFHS is limited in its ability to detect increases in risks of rare diseases because of the small size of the Ranch Hand population.

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15 NEUROLOGY ASSESSMENT

15.1 INTRODUCTION

Neurological signs and symptoms, as distinguished from overt diagnosable neurological disease, have been consistently associated with industrial exposure to chlorophenols, phenoxy herbicides, and dioxin. Animal research and studies of humans exposed to high levels of dioxin imply that the peripheral nervous system is a target organ for acute dioxin toxicity. The recognized acute neurotoxicity of these chemicals and the prevalence of neurological complaints among veterans are primary factors in the decision to place a major emphasis on the neurological evaluation of participants in the Air Force Health Study (AFHS).

Analyses were performed to assess the neurological function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). The neurology assessment was based on extensive physical examination data on cranial nerve function, peripheral nerve status, and central nervous system (CNS) coordination processes. This information was supplemented by verified histories of neurological diseases.

The questionnaire captured data on the occurrence of neurological disorders. Medical records reviews were conducted to confirm reported neurological conditions and to identify any unreported conditions for each participant. Neurological diseases and disorders were classified into four categories: hereditary and degenerative diseases, inflammatory diseases, peripheral disorders, and other neurological disorders.

The physical examination included various indicators of cranial nerve function, peripheral nerve status, and CNS coordination processes. The evaluation of cranial nerve function was based on the following 15 variables: balance, facial sensation, smell, visual fields, light reaction, ocular movement, corneal reflex, jaw clench, smile, palpebral fissure, gag reflex, speech, tongue position relative to midline, palate and uvula movement, and shoulder shrug. All of these variables were scored as normal or abnormal, except for jaw clench and palate and uvula movement, which were scored as symmetric or deviated. For variables with left and right determinations, the two results were combined to produce a single normal or abnormal result, where normal indicated that both responses were normal, and abnormal indicated that at least one of the responses was abnormal. Abnormal speech conditions included aphasia, dysarthria, agnosia, and other speech abnormalities. Associations between dioxin or herbicides and balance, facial sensation, smell, and visual fields were found and are discussed later in this chapter.

A cranial nerve index was created by combining responses for the 15 cranial nerve determinations. This index was classified as abnormal if at least one of the determinations was abnormal, and was classified as normal if all of the cranial nerve parameters were normal. Analyses in 1985, 1987, and 1992 investigated the effects of neck range of motion in conjunction with the cranial nerve index. The examining neurologist asked each participant to move his head to the left, right, and to tilt his head forward and backward. This test assessed the musculoskeletal and vertebral column function. This neck range of motion variable was coded as abnormal if there was a decreased range of motion forward or backward or to the left or right.

Peripheral nerve status was assessed by light touch (cotton sticks), visual inspection of muscle mass (and palpation, if indicated), light pinprick, three deep tendon reflexes (patellar, Achilles, and biceps), and the Babinski reflex. Pinprick and light touch were considered normal if the reaction was normal on both legs. A variable to judge muscle status was constructed using data on bulk; tone of upper and lower

extremities; and the strength of distal wrist extensors, ankle and toe flexors, proximal deltoids, and hip flexors. Bulk was classified as either normal or abnormal. Tone was classified as abnormal if there was either a decreased or increased response on either the left side, right side, or both sides. The strength of distal wrist extensors, ankle and toe flexors, proximal deltoids, and hip flexors was considered abnormal if either the left or right side or both sides were decreased. Composite muscle status was classified as normal if all of the components were normal on both the left and right sides and abnormal if at least one of the components was abnormal on either or both sides.

The patellar, Achilles, and biceps reflexes were divided into three categories: “absent,” “sluggish,” and “active or very active.” The categories of “active” and “very active” were combined because of the sparse number of participants with very active reflexes. Two contrasts that preserved the ordinal structure of the data were examined: “sluggish or absent” versus “active or very active” (i.e., less than active versus active), and “absent” versus “sluggish, active, or very active” (i.e., reflexes absent versus not absent). When the assessments of the reflex were different between the left and right body side, the more severe condition was assigned. For example, if the left Achilles reflex was sluggish and the right Achilles reflex was absent, the composite Achilles reflex variable was designated as absent.

Indices to assess signs and degree of polyneuropathy also were constructed from the neurologist’s assessment of the following seven parameters and a vibrotactile threshold measurement:

- Ankle and toe flexors
- Balance
- Achilles reflexes
- Light touch
- Pinprick
- Ankle vibration
- Position of great toe.

The evaluation of CNS coordination processes was based on the analyses of Romberg sign, coordination, gait, tremor, and a CNS index. For these variables, multiple determinations, which included left and right, as well as upper and lower responses, were combined to form a single result. A result was classified as normal if all determinations were normal and abnormal if at least one determination was abnormal. Tremor was examined for the left and right upper and lower extremities. Abnormal tremors included resting, essential, intention, and other tremors. Coordination was a composite index defined as normal if the Romberg sign, finger-nose-finger and heel-knee-shin coordination processes, rapidly alternating movements of pronation and supination of hands, and rapid patting were normal. The Romberg sign variable was equivalent to the “balance” variable analyzed as part of the cranial nerve function assessment. The gait variable was based on the examining physician’s assessment of the participant’s gait. An abnormal gait included conditions such as broad-based, small-stepped, ataxic, or other irregular gait patterns. A CNS index was constructed and based on a composite variable of tremor, coordination, and gait. This index was coded as normal if all three of the components were normal and abnormal if otherwise.

The following journal article on polyneuropathy in AFHS veterans was written by AFHS staff and their colleagues:

- Serum dioxin and peripheral neuropathy in veterans of Operation Ranch Hand (8).

This article is discussed later in this chapter.

In the 1996 Institute of Medicine (IOM) *Veterans and Agent Orange* update (9), the committee concluded that there is “limited/suggestive” evidence of an association between exposure to certain herbicides used in Vietnam and the development of an acute or subacute transient peripheral neuropathy. This conclusion remained unaltered in the 2002 and 2004 IOM *Veterans and Agent Orange* update (10, 11). The evidence regarding the association between exposure to dioxin and disorders involving persistent peripheral neuropathy, or motor or coordination deficits, was considered inadequate or insufficient (10, 11).

In the 1994 *Veterans and Agent Orange* report (12), the IOM concluded that there was inadequate or insufficient evidence to determine whether an association existed between dioxin and motor coordination problems. This conclusion remained unchanged in the 2004 *Veterans and Agent Orange* update (11).

A persisting concern exists about the role of herbicides and pesticides in the pathogenesis of Parkinson’s disease. The relation between pesticide exposure and Parkinson’s disease was evaluated in the 1996, 1998, 2000, 2002, and 2004 *Veterans and Agent Orange* update (9-11, 13-14). Some indication of an association between Parkinson’s disease and herbicides and pesticides was seen based on a review of 30 epidemiologic studies, most of which were case-control studies focusing on occupational exposure. An association of Parkinson’s disease with exposure to dioxin, however, was not reported in any of these studies. Therefore, the 2002 IOM committee considered the evidence for an association of Parkinson’s disease with exposure to dioxin to be inadequate or insufficient (10), and this conclusion was unchanged in the 2004 *Veterans and Agent Orange* update (11).

15.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this stratification based on the participant’s tour of duty is given in Chapter 2.

123 The following chart lists the variables that were analyzed for the neurology assessment and at which
 124 physical examination they were analyzed. The variables appearing in bold type are discussed
 125 subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Achilles Reflex	X	X	X	X	X	X	X
Babinski Reflex	X	X	X	X	X	X	X
Balance/Romberg Sign	X	X	X	X	X	X	X
Biceps Reflex	X	X	X	X	X	X	X
CNS Index		X	X	X	X	X	X
Conduction Velocity – Distal Ulnar	X						
Conduction Velocity – Peroneal	X						
Conduction Velocity – Proximal Ulnar	X						
Confirmed Polyneuropathy Index						X	
Coordination	X	X	X	X	X	X	X
Corneal Reflex	X	X	X	X	X	X	X
Cranial Nerve Index		X	X	X	X	X	X
Disorders of the Ear	X	X	X				
Disorders of the Eye	X	X	X	X			
Facial Sensation	X	X	X	X	X	X	X
Gag Reflex	X	X	X	X	X	X	X
Gait	X	X	X	X	X	X	X
Hearing Loss				X			
Hereditary and Degenerative Neurological Disease	X	X	X	X	X	X	X
Inflammatory Neurological Disease	X	X	X	X	X	X	X
Jaw Clench	X	X	X	X	X	X	X
Light Reaction	X	X	X	X	X	X	X
Light Touch	X	X	X	X	X	X	X
Multiple Polyneuropathy Index						X	
Muscle Status	X	X	X	X	X	X	X
Neck Range of Motion	X	X	X	X	X	X	
Ocular Movement	X	X	X	X	X	X	X
Other Neurological Disorders		X	X	X	X	X	X
Otitis				X			
Palate and Uvula Movement	X	X	X	X	X	X	X
Palpebral Fissure	X	X	X	X	X	X	X
Patellar Reflex	X	X	X	X	X	X	X
Peripheral Disorders	X	X	X	X	X	X	X
Pinprick	X	X	X	X	X	X	X
Polyneuropathy Prevalence Indicator						X	X
Polyneuropathy Severity Index						X	
Possible Peripheral Neuropathy							X
Probable Peripheral Neuropathy							X
Shoulder Shrug							X
Smell	X	X	X	X	X	X	X

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Smile	X	X	X	X	X	X	X
Speech	X	X	X	X	X	X	X
Tongue Position Relative to Midline	X	X	X	X	X	X	X
Tremor	X	X	X	X	X	X	X
Tympanic Membrane Disorder				X			
Vibration	X	X	X	X			
Vibrotactile Threshold Measurement of Great Toes					X		
Visual Fields	X	X	X	X	X	X	X

15.2 HEREDITARY AND DEGENERATIVE NEUROLOGICAL DISEASE

Based on data collected at the 2002 follow-up examination, more Ranch Hand officers than Comparison officers had hereditary and degenerative disorders after service in Southeast Asia (SEA).

15.3 INFLAMMATORY NEUROLOGICAL DISEASE

Based on data collected at the 1997 follow-up examination, more Ranch Hands than Comparisons had inflammatory diseases after service in SEA. The prevalence of inflammatory diseases also was increased in the background, low, and high dioxin categories. The increase in Ranch Hands was due to seven Ranch Hands and one Comparison who have had an inflammatory disease since service in SEA. Further review of these diseases revealed that three of the seven Ranch Hands had meningitis caused by bacterial infection. The Comparison had encephalitis of unknown cause. This review suggested that this finding was unrelated to herbicide or dioxin exposure. At the 2002 follow-up examination, nine Ranch Hands and seven Comparisons were verified to have had an inflammatory disease since service in SEA, but no differences between the two groups were detected.

15.4 PERIPHERAL DISORDERS

At the 1992 follow-up examination, among moderate lifetime drinkers (>0-40 drink-years), the prevalence of peripheral disorders after service in SEA increased with increasing levels of 1987 dioxin. The same relation between peripheral disorders and 1987 dioxin was seen in 1997 for all Ranch Hands.

15.5 OTHER NEUROLOGICAL DISORDERS

The majority of other neurological disorders were unspecified encephalopathies, but conditions such as multiple sclerosis and other demyelinating diseases of the CNS, hemiplegia, other paralytic syndromes, epilepsy, migraine, catalepsy or narcolepsy, other conditions of the brain, and other unspecified disorders of the CNS were included.

Based on data collected at the 1987 follow-up examination, as 1987 dioxin increased in Ranch Hands with later tours of duty, the prevalence of other neurological disorders after service in SEA increased. This pattern also was seen between initial dioxin and other neurological disorders after service in SEA.

15.6 CRANIAL NERVE FUNCTION

15.6.1 Balance/Romberg Sign

The prevalence of an abnormal balance determination in Ranch Hands at the 2002 follow-up examination increased as initial dioxin increased.

15.6.2 Facial Sensation

More Ranch Hands in the low dioxin category had an abnormal facial sensation at the 2002 follow-up examination than Comparisons.

15.6.3 Smell

Among participants who did not report exposure to insecticides, more Ranch Hand participants in the low dioxin category had an abnormal sense of smell at the 1992 follow-up examination than Comparisons.

15.6.4 Visual Fields

Among Ranch Hands who participated in the 1997 follow-up examination, the prevalence of abnormal visual fields increased as initial dioxin levels increased. At the 2002 follow-up examination, more Ranch Hands than Comparisons had abnormal visual fields. In particular, the increase appeared to be for Ranch Hands with background dioxin levels relative to Comparisons.

15.6.5 Neck Range of Motion

The prevalence of a neck range of motion abnormality at the 1987 follow-up examination increased for Ranch Hand diabetics (2-hour postprandial glucose ≥ 200 mg/dL or previously diagnosed as diabetic by a physician) as initial dioxin increased. Ranch Hands with earlier tours of duty showed an increase in neck range of motion abnormalities as 1987 dioxin levels increased.

The prevalence of a neck range of motion abnormality was increased for Ranch Hands at the 1997 follow-up examination. This pattern was seen when all participants were analyzed and when analyses were restricted to enlisted flyers. The increase also was observed in the low and high Ranch Hand dioxin categories relative to Comparisons.

15.6.6 Cranial Nerve Index

The results for the cranial nerve index at the 1987 follow-up examination were similar to neck range of motion. Neck range of motion abnormalities were included in the definition of the cranial nerve index for analysis at this examination and were the primary source of abnormalities for this index.

Analysis of 1987 follow-up examination data also was done without including neck range of motion in the definition of the cranial nerve index. Ranch Hands who did not report exposure to insecticides had more abnormalities on the index without including neck range of motion than Comparisons who did not report exposure to insecticides. When categorizing Ranch Hands according to dioxin levels, these differences between Ranch Hands and Comparisons were seen primarily in the low Ranch Hand dioxin category.

Analyses without including neck range of motion in the definition of the cranial nerve index also were performed for the 1992 follow-up examination. The prevalence of an abnormal index in Ranch Hands

with normal glucose levels (2-hour postprandial glucose < 140 mg/dL) increased as initial dioxin levels increased. In addition, Ranch Hand enlisted groundcrew had a higher prevalence of abnormalities than Comparison enlisted groundcrew; this increase in Ranch Hands was seen in the background and high dioxin categories.

Analysis for the cranial nerve index was done for the 2002 follow-up examination without considering neck range of motion. Ranch Hands showed a higher prevalence of an abnormal index than Comparisons, as did Ranch Hands in the background and low dioxin categories.

15.7 PERIPHERAL NERVE STATUS

15.7.1 Muscle Status

More Ranch Hand enlisted groundcrew than Comparison enlisted groundcrew had an abnormal muscle status at the 1997 follow-up examination.

15.7.2 Pinprick

Pinprick was considered normal if the reaction was normal on both feet and abnormal if the reaction was abnormal on either foot. At the 1987 follow-up examination for Ranch Hands with earlier tours of duty, the prevalence of an abnormal reaction to pinprick increased as 1987 dioxin increased. For Ranch Hands who were considered diabetic (2-hour postprandial glucose \geq 200 mg/dL or previously diagnosed as diabetic by a physician), the prevalence of an abnormal reaction to pinprick at the 1992 follow-up examination increased as 1987 dioxin increased. At the 2002 follow-up examination, Ranch Hands in the high dioxin category had an increased abnormal reaction to pinprick.

15.7.3 Achilles Reflex

The classification of the status of the Achilles reflex was divided into three categories: absent, sluggish, and active or very active. The categories of active and very active were combined because of the sparse number of participants with very active Achilles reflexes. When the assessments of the Achilles reflex were different between the left and right body side, the more severe condition was assigned.

A greater prevalence of Ranch Hand nondrinkers in the high dioxin category had an absent Achilles reflex at the 1992 follow-up examination than Comparison nondrinkers. At the 2002 follow-up examination, Ranch Hand officers had an absent or sluggish Achilles reflex more often than Comparison officers.

15.7.4 Patellar Reflex

The classification of the status of the patellar reflex was divided into three categories: absent, sluggish, and active or very active. The categories of active and very active were combined because of the sparse number of participants with very active patellar reflexes. When the assessments of the patellar reflex were different between the left and right body side, the more severe condition was assigned.

The prevalence of Ranch Hands with an absent patellar reflex at the 1997 follow-up examination increased as initial dioxin levels increased. The percentage of participants with an absent patellar reflex at the 2002 follow-up examination was increased in Ranch Hands in the high dioxin category. As 1987 dioxin increased, the prevalence of Ranch Hands with an absent patellar reflex at both the 1992 and 2002 follow-up examinations increased.

15.8 POLYNEUROPATHY

For the 1997 follow-up examination, three indices to assess polyneuropathy were based on a severity index. These indices assessed bilateral abnormalities and were considered abnormal only if both the left and right determinations were abnormal. These indices were based on the following seven conditions or sets of conditions:

- Both left and right ankle and toe flexors were abnormal (no=0, yes=1)
- The Romberg sign (equilibratory) was abnormal (no=0, yes=1)
- Both left and right Achilles reflexes were absent (no=0, yes=1)
- Reaction to a light touch was abnormal on both the left and right feet (no=0, yes=1)
- Reaction to a pinprick was abnormal on both the left and right feet (no=0, yes=1)
- Both left and right ankle vibrations were abnormal (no=0, yes=1)
- The position of both the left and right great toe was abnormal (no=0, yes=1).

A polyneuropathy severity index, which ranged from 0 to 7, was constructed as the sum of the above seven scores. The polyneuropathy severity index was classified as mild (index = 0, 1, or 2), moderate (index = 3 or 4), or severe (index = 5, 6, or 7). A second index, termed a polyneuropathy prevalence indicator, was coded as abnormal if the polyneuropathy severity index was at least 1 and normal if the polyneuropathy severity index was 0. A third index, termed a multiple polyneuropathy index, was coded as “abnormal” if the polyneuropathy severity index was at least 2 and “normal” if the polyneuropathy severity index was 0 or 1.

In addition, a confirmed polyneuropathy index was constructed as follows:

If at least two of the following three conditions held,

- Both left and right Achilles reflexes were absent
- Reaction to a pinprick was abnormal on both the left and right feet
- Both left and right ankle vibrations were abnormal

and the minimum of the left and right toe averages (in log microns) was greater than 4.02, the confirmed polyneuropathy index was coded as abnormal. If the minimum vibrotactile measurement was less than or equal to 4.02, or no more than one of the above conditions was present, the confirmed polyneuropathy index was coded as normal. The value of 4.02 was determined by taking the minimum value of the left and right great toe average for each participant and using the 90th percentile of the minimum values for Comparisons.

Associations between these indices and dioxin that were found based on the 1997 follow-up examination data are described below.

15.8.1 Vibrotactile Threshold Measurement of the Great Toes

A vibrotactile measurement was performed as part of a collaborative effort with the National Institute of Dental and Craniofacial Research at the 1992 and 1997 follow-up examinations. A Vibratron II[®] device was used to measure vibrotactile threshold on both the left and right great toes. The Vibratron II[®] provided a noninvasive means of measuring the sensitivity to vibration of a participant's feet. The left and right great toes were analyzed separately. For each great toe, the average (in log microns) of four of

seven trials was determined. The four trials were those remaining after eliminating the results of the first of the seven trials and the high and low readings of the other six results following a method-of-limits protocol (15).

Among Ranch Hands exposed to heavy metals, the vibrotactile threshold level of the left and right great toes at the 1992 follow-up examination increased as initial dioxin increased. For Ranch Hands whose glucose levels were considered impaired ($140 \text{ mg/dL} \leq 2\text{-hour postprandial glucose} < 200 \text{ mg/dL}$), the vibrotactile threshold level of the left great toe increased as initial dioxin increased. Ranch Hands in the background dioxin category who were heavy drinkers (>40 lifetime drink-years) had a greater average vibrotactile threshold measurement of the right great toe than Comparisons who were heavy drinkers. Ranch Hands in the high dioxin category who were nondrinkers had a greater average vibrotactile threshold measurement of the right great toe than Comparisons who were nondrinkers. For Ranch Hands who worked with heavy metals, the vibrotactile threshold level of the right great toe increased as 1987 dioxin levels increased. For Ranch Hands who worked with vibrating power equipment or tools, the vibrotactile threshold level of the left great toe increased as 1987 dioxin levels increased.

15.8.2 Polyneuropathy Severity Index

The prevalence of a moderate polyneuropathy severity index at the 1997 follow-up examination was increased for Ranch Hands. Among Ranch Hands, the prevalence of a moderate polyneuropathy severity index at this examination increased with increasing initial dioxin and 1987 dioxin, and was increased for Ranch Hands in the high dioxin category.

15.8.3 Polyneuropathy Prevalence Indicator

The prevalence of an abnormal polyneuropathy prevalence indicator at the 1997 follow-up examination increased with increasing initial dioxin in Ranch Hands.

15.8.4 Multiple Polyneuropathy Index

The prevalence of an abnormal multiple polyneuropathy index at the 1997 follow-up examination increased with increasing initial dioxin in Ranch Hands. Ranch Hands in the high dioxin category also had an increased prevalence of polyneuropathy based on this index.

15.8.5 Confirmed Polyneuropathy Index

The prevalence of confirmed polyneuropathy, according to this index, at the 1997 follow-up examination increased with increasing initial dioxin in Ranch Hands. Ranch Hands in the high dioxin category also had an increased prevalence of confirmed polyneuropathy using this index.

15.8.6 Serum Dioxin and Peripheral Neuropathy in Veterans of Operation Ranch Hand

In a 2001 journal article, Michalek and colleagues (8) performed additional analysis on the study of polyneuropathy in AFHS veterans. Four indices to assess polyneuropathy were used:

- Any symmetrical peripheral abnormality
- Possible symmetric peripheral neuropathy
- Probable symmetric peripheral neuropathy
- Diagnosed peripheral neuropathy.

Any symmetrical peripheral abnormality was equivalent to the polyneuropathy prevalence indicator defined in Section 15.8 and described in Section 15.8.3. Diagnosed peripheral neuropathy was equivalent to the confirmed polyneuropathy index defined in Section 15.8 and described in Section 15.8.5. Possible symmetric peripheral neuropathy and probable symmetric peripheral neuropathy dealt with three outcomes first described in Section 15.8; that is,

- Both left and right Achilles reflexes were absent
- Reaction to a pinprick was abnormal on both the left and right feet
- Both left and right ankle vibrations were abnormal.

Possible symmetric peripheral neuropathy was defined to be present if at least one of the above three conditions held. Probable symmetric peripheral neuropathy was defined as present if at least two of the above three conditions held.

Data from the 1982, 1985, 1987, 1992, and 1997 examinations were analyzed using the categorized dioxin model described in Section 2.4.2. This model categorized Ranch Hands and Comparisons according to their estimated initial and 1987 dioxin levels into four categories: Comparisons, background Ranch Hands (1987 dioxin levels at or below 10 ppt), low Ranch Hands (1987 dioxin level greater than 10 ppt, initial dioxin level \leq 94 ppt), and high Ranch Hands (1987 dioxin level greater than 10 ppt, initial dioxin level $>$ 94 ppt).

The analysis of diagnosed peripheral neuropathy was restricted to data from the 1992 follow-up examination and the 1997 follow-up examination because vibrotactile threshold data were collected only at these examinations. Nerve conduction velocities, measured at the 1982 baseline examination, also were analyzed, but no associations with dioxin were found. The analysis of bilateral vibrotactile abnormalities also showed no relations with dioxin.

A consistent increased risk of all indices of peripheral neuropathy among Ranch Hand veterans in the high dioxin category at the 1997 follow-up examination was found. An increased risk of diagnosed peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of the great toes, in Ranch Hand veterans in the high dioxin category at the 1992 follow-up examination also was seen. Restricting the analysis to the enlisted veterans did not alter these results. The authors stressed that cautious interpretation of these results was appropriate until the relationship between pre-clinical diabetes mellitus and peripheral neuropathy had been further evaluated.

The first three indicators of polyneuropathy described above—any symmetrical peripheral abnormality, possible symmetric peripheral neuropathy, and probable symmetric peripheral neuropathy—were evaluated for participants who attended the 2002 physical examination (7). No associations between dioxin and these indicators were observed.

15.9 CENTRAL NERVOUS SYSTEM (CNS) COORDINATION PROCESSES

15.9.1 Coordination

Coordination was a composite index defined as normal if the Romberg sign, finger-nose-finger and heel-knee-shin coordination processes, rapidly alternating movements of pronation and supination of hands, and rapid patting were normal. Ranch Hands had a higher prevalence of a coordination abnormality at the 1987 follow-up examination than Comparisons. Further analysis on subsets of these participants showed that the increase was in Ranch Hand enlisted groundcrew who did report exposure to insecticides.

Ranch Hands in the high dioxin category had a higher prevalence of a coordination abnormality than Comparisons. In particular, the increase was most pronounced in older Ranch Hands and Comparisons. As 1987 dioxin in Ranch Hands with later tours of duty increased, the prevalence of a coordination abnormality at the 1987 follow-up examination increased. The prevalence of an abnormal coordination at the 2002 follow-up examination increased as initial dioxin increased.

15.9.2 Gait

The gait variable was based on the examining physician's assessment of the participant's gait. An abnormal gait included conditions such as broad-based, small-stepped, ataxic, or other irregular gait patterns. The prevalence of an abnormal gait at the 1992 follow-up examination among older Ranch Hands increased as initial dioxin increased.

15.9.3 Tremor

Tremor was examined for the left and right upper and lower extremities. Abnormal tremors included resting, essential, intention, and other tremors. As 1987 dioxin in older Ranch Hands with later tours of duty increased, the prevalence of an abnormal tremor at the 1987 follow-up examination increased.

15.9.4 CNS Index

A CNS index was constructed and based on a composite variable of tremor, coordination, and gait. This index was coded as normal if all three of the components were normal and abnormal if otherwise. Ranch Hands had more abnormalities of the CNS index at the 1985 follow-up examination than Comparisons. At the 1987 follow-up examination, the prevalence of an abnormal CNS index in Ranch Hands increased as initial dioxin increased, primarily among older Ranch Hands. As 1987 dioxin in Ranch Hands with later tours of duty increased, the prevalence of a CNS index abnormality at the 1987 follow-up examination increased.

15.10 CONCLUSION

Increased risk of peripheral neuropathy has been somewhat indicated in those personnel with the highest levels of dioxin. Some indication for an association with probable peripheral neuropathy was found in the 1985, 1992, and 1997 follow-up examinations. Although a dose-response pattern was somewhat inconsistent in those years, the highest risk was observed in the group with the highest dioxin levels, most notably in the 1997 follow-up examination.

In a 2001 journal article, Michalek and colleagues (8) performed additional analysis on the study of polyneuropathy in AFHS veterans. A consistent increased risk of all indices of peripheral neuropathy among Ranch Hand veterans in the high dioxin category at the 1997 follow-up examination was found. An increased risk of diagnosed peripheral neuropathy, incorporating bilateral vibrotactile abnormalities of the great toes, in Ranch Hand veterans in the high dioxin category at the 1992 follow-up examination also was seen. The authors stressed that cautious interpretation of these results was appropriate until the relationship between pre-clinical diabetes mellitus and peripheral neuropathy had been further evaluated.

In the 2002 follow-up examination, Ranch Hands in the high dioxin category had an increased risk for an abnormal pinprick examination and an absent patellar reflex. The risk of an absent patellar reflex increased as the 1987 dioxin level increased. The composite indices for assessing neuropathy, however, were weak and did not show the same associations that were present in the analysis of 1997 follow-up examination data.

380 Based on the results of the analysis of pinprick, balance, and the patellar reflex in the 2002 follow-up
381 examination, there was some limited support of an association between dioxin levels and neurological
382 disease related to the peripheral nerves. No consistent associations or clinical evidence, however, to
383 support a relation between dioxin and cranial nerve function or other CNS processes appeared.

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16 PSYCHOLOGY ASSESSMENT

16.1 INTRODUCTION

A wide array of psychological abnormalities or impairments has been attributed or alleged to occur following exposure to chlorophenols, phenoxy herbicides, and dioxin. Many Southeast Asia (SEA) veterans have expressed concern that exposure to herbicides has caused psychological and behavioral problems, as reflected by the Veterans Health Administration's Agent Orange Registry (1). Emotional illnesses or psychological abnormalities, however, are not recognized in the scientific community as primary clinical endpoints following exposure to chlorophenols, phenoxy herbicides, and dioxin. "Neurobehavioral effects" occasionally ascribed to such exposures have been, in fact, predominantly neurological symptoms for which causation is not disputed. Higher central nervous system functioning, in terms of cognitive skills and reactivity, may be temporarily or permanently impaired depending on the exposure and the ability to measure accurately the psychological changes.

Analyses were performed to assess the psychological function of Air Force Health Study (AFHS) participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (2-9). The psychology assessment was based on the Cornell Index and the Minnesota Multiphasic Personality Inventory (MMPI) in 1982 and the Cornell Medical Index (CMI) and the MMPI in 1985. Data from the Millon Clinical Multiaxial Inventory (MCMI) were analyzed for the 1987 follow-up examination report. The Symptom Checklist-90-Revised (SCL-90-R) was used at the 1987, 1992, 1997, and 2002 follow-up examinations. Central nervous system functional testing was accomplished using a modified Halstead-Reitan Battery in 1982 and 1985. Intelligence was measured by the Wechsler Adult Intelligence Scale in 1982 and reading skills were tested by the reading subtest of the Wide Range Achievement Test in 1982. Memory was tested by the Wechsler Memory Scale-Version 1 at the 1982 baseline examination and the Wechsler Memory Scale-Revised at the 2002 follow-up examination. Short descriptions of the Cornell Index, the CMI, the MCMI, the MMPI, and the SCL-90-R are provided in subsequent sections of this chapter.

The questionnaire captured data on the occurrence of mental or emotional disorders at each of the six AFHS examinations. Medical record reviews confirmed reported conditions and identified any unreported conditions for each participant. As a result, psychological disorders were classified into five categories: psychoses, alcohol dependence, drug dependence, anxiety, and other neuroses. In addition to this verified history of psychological disorders, self-reported responses to questions assessing anger, anxiety, fatigue, and isolation were analyzed for the 1982 baseline examination. Responses to a series of questions on 12 types of sleep problems were analyzed for the 1987 follow-up examination.

In addition to the eight reports (2-9), two journal articles were published based on the psychological data collected at the AFHS examinations. One article,

- Serum dioxin and psychological functioning in U.S. Air Force veterans of the Vietnam War (10),

related dioxin levels to data collected from the MMPI in 1982 and 1985 and from the MCMI in 1987 and 1992.

The other article,

- Serum dioxin and cognitive functioning in veterans of Operation Ranch Hand (11), related dioxin to cognitive function measures from the Halstead-Reitan Battery, the Wechsler Adult Intelligence Scale, and the Wechsler Memory Scale.

In the Institute of Medicine (IOM) 2004 *Veterans and Agent Orange* update (12), the committee concluded that there is “inadequate or insufficient” evidence of an association between exposure to certain herbicides used in Vietnam and cognitive or neuropsychiatric disorders.

16.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand’s last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this stratification based on the participant’s tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the psychology assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Alcohol Dependence	X	X	X	X	X	X	X
Anxiety	X	X	X	X	X	X	X
Cornell Index (Overall and 10 Scales):	X						
Cornell Medical Index (3 Scores)		X					
Drug Dependence			X	X	X	X	X
Halstead-Reitan Battery Impairment Index	X	X					

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
MCMI (20 Scales)			X	X			
MMPI (14 Scales)	X	X					
Other Neuroses	X	X	X	X	X	X	X
Psychoses	X	X	X	X	X	X	X
Questionnaire Indices (Anger, Anxiety, Depression [Severity], Erosion, Fatigue, Isolation)	X						
SCL-90-R (12 Scales)			X	X	X	X	X
<i>Sleep Disorders:</i>							
Abnormal Movement/Activity During the Night			X	X			
Average Sleep Each Night			X	X			
Frightening Dreams			X	X			
Great or Disabling Fatigue During the Day			X	X			
Insomnia			X	X			
Involuntarily Falling Asleep During the Day			X	X			
Overall Sleep Disorder Index			X	X			
Sleep Problems Requiring Medication			X	X			
Sleepwalking			X	X			
Snore Loudly in All Sleeping Positions			X	X			
Talking in Sleep			X	X			
Trouble Falling Asleep			X	X			
Waking Up During the Night			X	X			
Waking Up Too Early and Can't Go Back to Sleep			X	X			
Waking Up Unrefreshed			X	X			
Wechsler Adult Intelligence Scale (Verbal, Performance, and Full Scale)	X						
WMS-R Memory Tests (5 Scores)							X

16.2 ALCOHOL DEPENDENCE

As of the 1992 follow-up examination, married enlisted groundcrew Ranch Hands showed a higher prevalence of alcohol dependence after service in SEA than married enlisted groundcrew Comparisons.

16.3 OTHER NEUROSES

At the health interview during the six AFHS examinations, each participant was asked whether he had a mental or emotional disorder since the date of his last interview. The category of disorders named "other neuroses" included the following conditions:

- Neurotic disorders, comprising hysteria, phobic disorders, obsessive-compulsive disorders, neurotic depression, neurasthenia, hypochondriasis, other neurotic disorders, and unspecified neurotic disorders
- Personality disorders

- Sexual deviations and disorders
- Nondependent abuse of drugs
- Physiological malfunction arising from mental factors
- Special symptoms or syndromes not elsewhere classified
- Acute reaction to stress
- Adjustment reaction
- Depressive disorder not elsewhere classified.

Based on data at the 1987 follow-up examination, Ranch Hands in the low dioxin category exhibited a higher prevalence of other neuroses than Comparisons after service in SEA.

Among enlisted groundcrew personnel, participants with at most a high school education, and participants in higher income households, Ranch Hands showed a higher prevalence of other neuroses at the 1992 follow-up examination than Comparisons after service in SEA. Among participants with at most a high school education, Ranch Hands in the background and low dioxin categories also showed a higher prevalence of other neuroses than Comparisons after service in SEA. Among participants in higher income households, Ranch Hands in the high dioxin category showed a greater prevalence of other neuroses than Comparisons after service in SEA.

Based on data collected at the 1997 follow-up examination, Ranch Hand enlisted groundcrew had a higher prevalence of other neuroses than Comparison enlisted groundcrew after service in SEA. Ranch Hands in the low dioxin category also exhibited a higher prevalence of other neuroses than Comparisons after service in SEA. Based on data collected at the 1997 follow-up examination, further analysis of other neuroses by the individual categories provided above showed no predominance of any one category (8).

16.4 ANGER, ANXIETY, FATIGUE, AND ISOLATION

Questionnaire response from the 1982 baseline examination concerning anger, anxiety, fatigue, and isolation showed higher levels of these parameters for Ranch Hands than Comparisons in participants with at most a high school education, but not in participants with a college education.

16.5 SLEEP PROBLEMS

Each participant was asked a series of questions on whether he had a current or past problem with 12 different sleep disorders (13). Associations between frightening dreams and average sleep each night and dioxin were observed at the 1987 follow-up examination and are discussed below.

Based on data collected at the 1987 follow-up examination, Ranch Hands in the high dioxin category had a greater prevalence of past or present problems with frightening dreams. In addition, as 1987 dioxin increased for Ranch Hands with later tours of duty, the prevalence of past or present problems with frightening dreams increased.

Based on information reported by participants at the 1987 follow-up examination, the average number of hours of sleep each night decreased as 1987 dioxin increased among Black participants with earlier tours of duty.

16.6 CORNELL INDEX

The Cornell Index (14) was a subjective 10- to 15-minute self-administered inventory of neuropsychiatric symptoms and complaints given only at the 1982 baseline examination. Among those participants with at most a high school education, Ranch Hands had a greater (adverse effect) average total Cornell index score than Comparisons.

16.7 CORNELL MEDICAL INDEX (CMI)

The CMI (15) was a self-administered instrument used only at the 1985 follow-up examination to collect a substantial amount of medical and psychiatric data. The 195 questions of the CMI were partitioned into 18 sections (A-R), with the number of questions within a section ranging from 6 to 23. Three scores were derived from the CMI: the total CMI score, an A-H area subscore, and an M-R subscore. The A-H subscore was a measure of the scatter of complaints, indicating a diffuse medical problem, although other interpretations were possible. The M-R subscore, which deals with mood and feeling patterns, was a useful indicator of emotional ill health. The total CMI score was the number of affirmative responses on the entire CMI questionnaire.

Ranch Hands had a higher (adverse effect) average A-H area subscore than Comparisons. Among those participants with at most a high school education, Ranch Hands had a higher average total CMI score than Comparisons.

16.8 MILLON CLINICAL MULTIAXIAL INVENTORY (MCMI)

The MCMI (16), a self-administered test comprising 175 items and divided into 20 scales, was used only at the 1987 AFHS follow-up examination. Each of its 20 scales was constructed as an operational measure of a syndrome derived from a theory of personality and psychopathology. The MCMI was not designed to be a general personality instrument to be used for “normal” populations or for purposes other than diagnostic screening or clinical assessment. The 20 scales were organized into three broad categories to reflect distinctions between basic personality patterns, pathological personality disorders, and clinical symptom syndromes. Many of these scales were directly or indirectly correlated. Higher MCMI scores represented an adverse effect. All results provided in Sections 16.8.1 through 16.8.17 are based on data reported from the 1987 follow-up examination.

Eight scales from the MCMI focused on everyday ways of functioning that characterized participants even when they were not suffering acute symptom states. These eight scales are antisocial (aggressive), avoidant, compulsive (conforming), dependent (submissive), histrionic (gregarious), narcissistic, passive-aggressive (negativistic), and schizoid (asocial), all of which are discussed in Sections 16.8.1 through 16.8.8.

Three MCMI scales described patients who clearly evidence chronic or periodically severe pathology in the overall structure of personality. These scales are borderline (cycloid), paranoid, and schizotypal (schizoid), all of which are discussed in Sections 16.8.9 through 16.8.11.

Nine scales from the MCMI measured reactive disorders, often precipitated by external events, that are of substantially briefer duration than the personality disorders. Six scales—alcohol abuse, anxiety, drug abuse, dysthymic, hypomanic, and somatoform—represented disorders of moderate severity. Except for drug abuse, where no adverse effects to Ranch Hands were found, the other five scales are discussed below in Sections 16.8.12 through 16.8.16. The other three scales—psychotic delusions, psychotic depression, and psychotic thinking—reflected disorders of marked severity. The psychotic depression

score is discussed below in Section 16.8.17. No adverse effects to Ranch Hands were found for psychotic delusions and psychotic thinking.

A summary of a journal article published in 2003 (10) that relates the MCMI results to dioxin levels is provided in Section 16.8.18.

16.8.1 Antisocial

Ranch Hands in the background dioxin category who were heavy drinkers (more than four drinks per day) had a higher average MCMI antisocial score than Comparisons who were heavy drinkers. In addition, Ranch Hands in the low dioxin category who were light drinkers (no more than one drink per day) had a higher average MCMI antisocial score than Comparisons who were light drinkers.

16.8.2 Avoidant

The MCMI avoidant score increased as initial dioxin increased. This relation between the MCMI avoidant score and initial dioxin was present when all Ranch Hands were examined and when analysis was restricted to college-educated Ranch Hands. In addition to the relation with initial dioxin, an association between the MCMI avoidant score and 1987 dioxin levels was observed in Ranch Hands with earlier tours of duty.

16.8.3 Compulsive

For participants who were heavy drinkers, Ranch Hands had a higher average MCMI compulsive score than Comparisons.

16.8.4 Dependent

The MCMI dependent score in Ranch Hands increased as initial dioxin increased and as 1987 dioxin levels increased in Ranch Hands with earlier tours of duty.

16.8.5 Histrionic

The MCMI histrionic score increased as initial dioxin increased in Black Ranch Hands with later tours of duty.

16.8.6 Narcissistic

Ranch Hands had a higher average MCMI narcissistic score than Comparisons.

16.8.7 Passive-aggressive

Among participants with at most a high school education, Ranch Hands had a higher average MCMI passive-aggressive score than Comparisons. Younger Ranch Hands in the background dioxin category also had a higher average MCMI passive-aggressive score than younger Comparisons.

16.8.8 Schizoid

Among nondrinkers and moderate drinkers (no more than 40 lifetime drink-years), the MCMI schizoid score in Ranch Hands with earlier tours of duty increased as 1987 dioxin increased. The MCMI schizoid score also increased as initial dioxin in Ranch Hands increased.

16.8.9 Borderline

The MCMI borderline score increased as initial dioxin increased in college-educated Ranch Hands.

16.8.10 Paranoid

Ranch Hands had a higher average MCMI paranoid score than Comparisons.

16.8.11 Schizotypal

The MCMI schizotypal score increased as initial dioxin in Ranch Hands increased and as 1987 dioxin increased in Ranch Hands with earlier tours of duty.

16.8.12 Alcohol Abuse

The average MCMI alcohol abuse score for Black Ranch Hands in the background and high dioxin categories was higher than the average MCMI alcohol abuse score for Black Comparisons.

16.8.13 Anxiety

Black Ranch Hands had a higher average MCMI anxiety score than Black Comparisons. Black Ranch Hands in the background dioxin category also had a higher average MCMI anxiety score than Black Comparisons. An association between the MCMI anxiety score and initial dioxin was observed in non-Black Ranch Hands. As initial dioxin increased, the MCMI anxiety score increased for non-Black Ranch Hands.

16.8.14 Dysthymia

The MCMI dysthymia score in non-Black Ranch Hands increased as initial dioxin increased.

16.8.15 Hypomania

The MCMI hypomania score in Black Ranch Hands increased as initial dioxin increased. The average MCMI hypomania score also was increased in Black Ranch Hands in the high dioxin category relative to Black Comparisons.

16.8.16 Somatoform

The MCMI somatoform score increased as 1987 dioxin levels in Ranch Hands with later tours of duty increased and as initial dioxin in Ranch Hands increased.

16.8.17 Psychotic Depression

The MCMI psychotic depression score increased as initial dioxin in Ranch Hands increased and as 1987 dioxin levels in Ranch Hands with earlier tours of duty increased.

16.8.18 Serum Dioxin and Psychological Functioning in U.S. Air Force Veterans of the Vietnam War: MCMI

A 2003 journal article related dioxin levels to data collected for the MCMI at the 1987 and 1992 follow-up examinations (10). Only Ranch Hands in the background dioxin category were more likely to have

elevated MCMI scale scores based on data from the 1992 follow-up examination. These elevations were primarily in the basic personality patterns. Ranch Hand veterans in the low and the high dioxin categories were similar to Comparisons in analysis of both the 1987 and 1992 follow-up examination data.

16.9 MINNESOTA MULTIPHASIC PERSONALITY INVENTORY (MMPI)

The MMPI is a self-administered test that was used at the 1982 and 1985 AFHS examinations. It comprises 566 questions on various aspects of behavior and personality (17). The results of the MMPI are numerical scores for 14 scales. The scales are anxiety (psychasthenia), consistency, defensiveness, denial, depression, hypochondria, hysteria, mania/hypomania, masculinity/femininity, paranoia, psychopathic/deviate, schizophrenia, social introversion, and validity. Differences between Ranch Hands and Comparisons at the 1982 and 1985 examinations are discussed in Sections 16.9.1 through 16.9.8. A summary of a journal article published in 2003 (10) that relates the MMPI results to dioxin levels is provided in Section 16.9.9.

16.9.1 Depression

Ranch Hands had a greater prevalence of high scores on the MMPI depression scale than Comparisons at the 1982 baseline examination.

16.9.2 Hypochondria

Ranch Hands had a greater prevalence of high scores on the MMPI hypochondria scale than Comparisons at the 1982 baseline examination.

16.9.3 Hysteria

Ranch Hands had a greater prevalence of high scores on the MMPI hysteria scale than Comparisons at the 1982 baseline examination.

16.9.4 Mania/Hypomania

Among participants with at most a high school education, Ranch Hands had a higher average MMPI mania/hypomania score than Comparisons at the 1982 baseline examination.

16.9.5 Masculinity/Femininity

Among participants with at most a high school education, Ranch Hands had a higher average MMPI masculinity/femininity score than Comparisons at the 1982 baseline examination.

16.9.6 Paranoia

Older Ranch Hands had a greater prevalence of abnormal scores on the MMPI paranoia scale than older Comparisons at the 1985 follow-up examination.

16.9.7 Schizophrenia

Ranch Hands with at most a high school education had a greater prevalence of abnormal scores on the MMPI schizophrenia scale at the 1985 follow-up examination than Comparisons with at most a high school education.

16.9.8 Social Introversion

Among participants with at most a high school education, Ranch Hands had a higher average MMPI social introversion score at the 1982 baseline examination than Comparisons. Ranch Hands had a greater prevalence of abnormal scores on the MMPI social introversion scale at the 1985 follow-up examination than Comparisons.

16.9.9 Serum Dioxin and Psychological Functioning in U.S. Air Force Veterans of the Vietnam War: MMPI

A 2003 journal article related dioxin levels to data collected for the MMPI at the 1982 and 1985 examinations (10). Few associations between dioxin levels and clinical elevations on the MMPI were seen based on data collected at the 1982 baseline examination. The direction and patterns of the associations were inconsistent. Ranch Hand veterans with higher dioxin levels showed some difficulties in anxiety, somatization, depression, and a denial of psychological factors. Ranch Hand veterans with background levels also showed indications of emotional distress, primarily in emotional numbing and lability; a guarded, suspicious, and withdrawn style of relating to others; and unusual thoughts or behaviors.

No positive associations between dioxin level and clinical elevations on the MMPI scales were observed based on data collected at the 1985 follow-up examination. No association between dioxin and post-traumatic stress disorder, as measured from questions on the MMPI, was observed at either the 1982 or 1985 AFHS examinations.

16.10 SYMPTOM CHECKLIST-90-REVISED (SCL-90-R)

Twelve variables were derived from the SCL-90-R, which comprises nine primary symptom categories and three global indices of distress. A short description of each of the primary symptom categories and global indices of distress, which was taken from the SCL-90-R reference manual (18), is given before the description of the results in each of the sections that follow. The function of the three global measures of the SCL-90-R—the global severity index, the positive symptom distress index, and the positive symptom total—was to communicate in a single score the level or depth of the individual's psychopathology. The SCL-90-R was a self-administered test taken by participants at the 1987, 1992, 1997, and 2002 follow-up examinations.

No associations showing an adverse effect to Ranch Hands or a positive association with dioxin were found for the primary symptom categories of interpersonal sensitivity and phobic anxiety and for the global indices of the positive symptom distress index and the positive symptom total. The primary symptom categories of anxiety, depression, hostility, obsessive-compulsive behavior, paranoid ideation, psychoticism, somatization, and the global severity index are discussed below.

16.10.1 Anxiety

The SCL-90-R anxiety dimension is a set of signs and symptoms that are associated clinically with high levels of manifest anxiety. General signs such as nervousness, tension, and trembling are included in the definition, as are panic attacks and feelings of terror. Cognitive components involving feelings of apprehension and dread, and some of the somatic correlates of anxiety, also are included as dimensional components. The symptoms comprising the anxiety dimension are experiencing nervousness or shakiness inside, trembling, being suddenly scared for no reason, feeling fearful, experiencing heart pounding or

298 racing, feeling tense and keyed up, having spells of terror and panic, feeling so restless you couldn't sit
299 still, feeling that something bad is going to happen, and experiencing frightening thoughts and images.

300 Based on data from the 1987 follow-up examination, the prevalence of high SCL-90-R anxiety scores
301 increased as 1987 dioxin increased in Ranch Hands with earlier tours of duty. This positive association
302 between SCL-90-R anxiety and 1987 dioxin also was seen at the 1992 follow-up examination for
303 participants who drank, on average, at most one drink per day.

304 **16.10.2 Depression**

305 The symptoms of the depression dimension reflect a broad range of the manifestations of clinical
306 depression. Symptoms of dysphoric mood and affect are represented, as are signs of withdrawal of life
307 interest, lack of motivation, and loss of vital energy. In addition, feelings of hopelessness, thoughts of
308 suicide, and other cognitive and somatic correlates of depression are included. The symptoms comprising
309 the depression dimension are losing sexual interest or pleasure, feeling low in energy or a slowing down,
310 thinking of ending your life, crying easily, feeling trapped or caught, blaming yourself for things, feeling
311 lonely, feeling blue, worrying too much about things, feeling no interest in things, feeling hopeless about
312 the future, feeling everything is an effort, and feeling worthless.

313 For moderate lifetime Ranch Hand drinkers (between 0 and 40 lifetime drink-years), the prevalence of
314 high SCL-90-R depression scores at the 1992 follow-up examination increased as initial dioxin increased.
315 Among Ranch Hands in higher income households and Black Ranch Hands, the prevalence of high SCL-
316 90-R depression scores also increased as 1987 dioxin increased.

317 **16.10.3 Hostility**

318 The hostility dimension reflects thoughts, feelings, or actions that are characteristic expressions of anger.
319 The items comprising the hostility dimension were selected to measure the three modes of manifestation
320 (i.e., thoughts, feelings, actions) and reflect qualities such as aggression, irritability, rage, and resentment.
321 The dimension's symptoms are feeling easily annoyed or irritated; having uncontrollable temper
322 outbursts; having urges to beat, injure, or harm someone; having urges to break or smash things; getting
323 into frequent arguments; and shouting or throwing things.

324 At the 1992 follow-up examination, for enlisted groundcrew who had at most a high school education,
325 Ranch Hands had a greater prevalence of high SCL-90-R hostility scores than Comparisons.

326 **16.10.4 Obsessive-compulsive Behavior**

327 The obsessive-compulsive dimension reflects symptoms that are highly identified with the standard
328 clinical syndrome of the same name. This measure focuses on thoughts, impulses, and actions that are
329 experienced as unrelenting and irresistible by the individual and inconsistent with the individual's own
330 beliefs about what is desirable or reasonable. Behaviors and experiences of a more general cognitive
331 performance attenuation also are included in this measure. The symptoms comprising the obsessive-
332 compulsive dimension are experiencing repeated unpleasant thoughts that won't leave the mind, having
333 trouble remembering things, worrying about sloppiness or carelessness, feeling blocked in getting things
334 done, having to do things very slowly to ensure correctness, having to check and double-check what is
335 done, having difficulty making decisions, having mind blanks, having trouble concentrating, and having
336 to repeat the same actions (e.g., touching, counting, washing).

Ranch Hands had a greater prevalence of high SCL-90-R obsessive-compulsive scores than Comparisons at the 1992 follow-up examination. In relation to dioxin levels, this difference was seen for Ranch Hands in the background dioxin category. An interaction between current alcohol use, household income, and 1987 dioxin also was observed in the analysis of SCL-90-R obsessive-compulsive scores.

16.10.5 Paranoid Ideation

The present dimension represents paranoid behavior fundamentally as a disordered mode of thinking. The cardinal characteristics of projective thought, hostility, suspiciousness, grandiosity, centrality, fear of loss of autonomy, and delusions are viewed as primary reflections of this disorder; item selection was oriented toward representing this conceptualization. The symptoms comprising the paranoid ideation dimension are feeling others are to blame for most of your troubles, feeling that most people cannot be trusted, feeling that you are watched or talked about by others, having ideas and beliefs that others do not share, not receiving proper credit from others for your achievements, and feeling that people will take advantage of you if you let them.

At the 1992 follow-up examination, for non-Black enlisted personnel, Ranch Hands had a greater prevalence of high SCL-90-R paranoid ideation scores than Comparisons. Ranch Hands in the background dioxin category also had a greater prevalence of high SCL-90-R paranoid ideation scores than Comparisons.

16.10.6 Psychoticism

The psychoticism scale was developed in a fashion to represent the construct as a continuous dimension of human experience. Items indicative of a withdrawn, isolated, schizoid lifestyle were included, as were Schneiderian first-rank symptoms of schizophrenia, such as hallucinations and thought broadcasting. The symptoms comprising the psychoticism dimension are having the idea that someone else can control your thoughts, hearing voices that other people do not hear, believing that other people are aware of your private thoughts, having thoughts that are not your own, feeling lonely even when you are with people, having thoughts about sex that are continuously bothersome, believing that you should be punished for your sins, thinking that something serious is wrong with your body, never feeling close to another person, and thinking that something is wrong with your mind.

Among moderate and heavy current drinkers (greater than one drink per day, on average), Ranch Hands in the background dioxin category had a greater prevalence of high SCL-90-R psychoticism scores than Comparisons at the 1992 follow-up examination.

16.10.7 Somatization

The somatization dimension reflects distress arising from perceptions of bodily dysfunction. Complaints focusing on cardiovascular, gastrointestinal, respiratory, and other systems with strong autonomic mediation are included. Headaches, pain, and discomfort of the gross musculature and additional somatic equivalents of anxiety are components of the definition. These symptoms and signs have all been demonstrated to have high prevalence in disorders demonstrated to have a functional etiology, although all may be reflections of true physical disease. The symptoms comprising the somatization dimension are headaches, faintness or dizziness, pains in heart or chest, pains in lower back, nausea or upset stomach, soreness of muscles, trouble getting breath, hot or cold spells, numbness or tingling in parts of body, lump in throat, weakness in parts of body, and heavy feelings in arms or legs.

Ranch Hands with at most a high school education had a greater prevalence of high SCL-90-R somatization scores than Comparisons with at most a high school education at the 1987 follow-up examination.

At the 1992 follow-up examination, more Ranch Hands than Comparisons had high SCL-90-R somatization scores. In particular, the increase appeared to be for Ranch Hands with background dioxin levels relative to Comparisons. Among Ranch Hands with a college education, the prevalence of high SCL-90-R somatization scores at the 1992 follow-up examination increased as 1987 dioxin increased.

16.10.8 Global Severity Index

The global severity index represents the best single indicator of the current level or depth of the disorder and should be used in most instances in which a single summary measure is required. The global severity index combines information on numbers of symptoms and intensity of perceived distress.

Among non-Black Ranch Hands with earlier tours of duty at the 1987 follow-up examination, the prevalence of high SCL-90-R global severity index scores increased as 1987 dioxin increased.

Ranch Hands had a higher prevalence of high SCL-90-R global severity index scores than Comparisons at the 1992 follow-up examination. Among Ranch Hands who drank less than one alcoholic drink per day, the prevalence of high SCL-90-R global severity index scores at the 1992 follow-up examination increased with both initial and 1987 dioxin. In addition, among Ranch Hands in higher income households, the prevalence of high SCL-90-R global severity index scores at the 1992 follow-up examination increased as 1987 dioxin increased.

16.11 SERUM DIOXIN AND COGNITIVE FUNCTIONING IN VETERANS OF OPERATION RANCH HAND

The Halstead-Reitan Battery (19), the Wechsler Adult Intelligence Scale-Revised (20), the Wechsler Memory Scale (21), and the Wide Range Achievement Test (22) were used to assess cognitive functioning among Air Force veterans at the 1982 baseline examination. Measures of cognitive functioning from these tests were examined for associations with dioxin levels that were measured in 1987 and 1992. The results of these analyses are documented in a 2001 journal article (11) and are summarized below.

The results of this study suggested that, although there are not global decrements in cognitive functioning associated with dioxin exposure among Vietnam veterans, there may be specific decrements involving verbal and factual memory functioning. Based on the Wechsler Memory Scale administered at the 1982 baseline examination, there were decrements in tasks involving verbal memory functioning in Ranch Hands with the highest dioxin levels relative to Comparisons. The same pattern also was found in Ranch Hand enlisted personnel with reported skin exposure to herbicides, relative to enlisted Comparison personnel. The differences were relatively small, however, and of uncertain clinical meaning.

A revised version of the Wechsler Memory Scale (23) was administered at the 2002 follow-up examination. No differences in the memory scale between groups were found, and no associations between the memory scales and dioxin were observed.

Analysis of the Halstead impairment index as derived from the Halstead-Reitan Battery, which was a crude measure for categorizing brain damage, showed that Ranch Hand veterans with low dioxin exposure were more likely than Comparison veterans to be rated as severely impaired. The number of

veterans categorized as severely impaired, however, was small (n=64), and the average impairment score for Ranch Hand veterans was not different from Comparisons.

Ranch Hand veterans with low dioxin levels showed slower motor speed, as measured by the Halstead-Reitan finger-tapping test on both the dominant and the nondominant hand. Ranch Hand veterans with background dioxin levels showed decreased motor strength, as measured by the Halstead-Reitan grip strength test with the nondominant hand only. These results were of small and uncertain clinical meaning, with no clear dose-response pattern.

16.12 CONCLUSION

The 1982 baseline examination showed more differences between Ranch Hands and Comparisons (primarily those participants with at most a high school education) in subjective measurements rather than objective measurements. When multiple test instruments that measured similar variables were used, such as the SCL-90-R and the MCMI at the 1987 follow-up examination, there appeared to be a lack of consistency in the outcomes. Although differences between groups and associations with dioxin were seen in the psychological tests performed across the six examinations, no clear patterns were discernible.

Although differences between Ranch Hands with the highest dioxin levels and Comparisons were seen for tasks involving verbal memory functioning at the 1982 baseline examination, these differences were not observed at the 2002 follow-up examination.

Psychological disorders that were verified by medical records review and the SCL-90-R were analyzed for the follow-up examinations in 1987, 1992, 1997 and 2002. Except for other neuroses, based on data at the 1997 follow-up examination, no adverse effects to Ranch Hands or associations with dioxin were found. In summary, there does not appear to be any clear evidence of disorders or syndromes that can be associated with exposure to herbicides and dioxin.

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17 PULMONARY ASSESSMENT

17.1 INTRODUCTION

Pulmonary dysfunction and overt pulmonary disease are not recognized clinical entities resulting from exposure to chlorophenols, phenoxy herbicides, or dioxin. Acute exposure to chlorophenols, phenoxy herbicides, and dioxin has caused the traditional acute symptoms of cough, nasal/lung irritation, shortness of breath, and occasionally, bronchitis. These acute effects and the high likelihood of inhalation exposure to herbicides among the operation Ranch Hand personnel in Vietnam prompted the evaluation of the pulmonary status of Air Force Health Study (AFHS) participants.

Analyses were performed to assess the pulmonary function of AFHS participants at the 1982, 1985, 1987, 1992, 1997, and 2002 examinations (1-7). In the self-administered family and personal history section, each study participant was asked whether he had ever experienced asthma, bronchitis, pleurisy, pneumonia, or tuberculosis. Medical records reviews were conducted to confirm reported pulmonary conditions and to identify any unreported conditions for each participant.

Part of the pulmonary assessment was based on the results of the physical examination of the thorax and lungs. A composite variable—thorax and lung abnormality—was constructed based on the presence or absence of asymmetrical expansion, hyperresonance, dullness, wheezes, rales, or chronic obstructive pulmonary disease, as well as the physician's assessment of abnormality. The individual conditions of asymmetrical expansion, hyperresonance, dullness, wheezes, and rales also were analyzed for the reports describing the 1985 and 1987 follow-up examinations.

The assessment of the laboratory examination data included the interpretation of pulmonary abnormalities detected on a routine chest x-ray film. This variable was coded as normal or abnormal. The assessment also included the analysis of pulmonary physiological data collected during the physical examination employing standard spirometry techniques. Numerous indices were derived, including forced vital capacity (FVC)—a measurement of the amount of air in liters expelled from maximum inspiration to full expiration—and forced expiratory volume in 1 second (FEV₁) in liters, an index derived from the FVC that quantifies the amount of air expelled in 1 second. The values used for these variables were the percentages of predicted values rather than the actual volume or flow rate. In addition, the ratio of observed FEV₁ to observed FVC was calculated as an index reflective of obstructive airway disease. For these indices, lower values indicated greater compromise in lung function. The FVC and the FEV₁ were based on the percent of predicted values, and the predicted values were adjusted for age and height. Loss of vital capacity and obstructive abnormality were classified by the examiner as none, mild, moderate, or severe.

The Institute of Medicine *Veterans and Agent Orange* reports, including the most recent 2004 update (8), consistently concluded that there is “inadequate or insufficient” evidence to determine the existence of an association between exposure to certain herbicides used in the Vietnam War and nonmalignant respiratory disorders.

17.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and

demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987 follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the "earlier" tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the "later" tour of duty throughout this chapter). Further discussion of this stratification based on the participant's tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the pulmonary assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
Asymmetrical Expansion		X	X	X			
Asthma		X	X	X	X	X	X
Bronchitis		X	X	X	X	X	X
Dullness		X	X	X			
FEV₁	X		X	X	X	X	X
FEV ₂			X				
FEV ₃			X				
Forced Expiratory Flow Maximum			X	X			
FVC	X		X	X	X	X	X
Hyperresonance		X	X	X			
Loss of Vital Capacity			X	X	X	X	X
Obstructive Abnormality			X	X	X	X	X
Pleurisy		X	X	X			
Pneumonia		X	X	X	X	X	X
Rales		X	X	X			
Ratio of Observed FEV₁ to Observed FVC	X		X	X	X	X	X
Thorax and Lung Abnormality		X	X	X	X	X	X
Tuberculosis		X	X	X			
Wheezes		X	X	X			
X-ray Interpretation		X	X	X	X	X	X

17.2 ASTHMA

Ranch Hands in the background dioxin category had a higher prevalence of asthma after service in Southeast Asia (SEA) than Comparisons at the time of the 1987 follow-up examination.

17.3 BRONCHITIS

In the enlisted flyer cohort and the background dioxin category, Ranch Hands had a higher prevalence of bronchitis after service in SEA than Comparisons in the analysis of the 1992 follow-up examination data.

17.4 PLEURISY

The prevalence of pleurisy after service in SEA was increased among Ranch Hands with a moderate lifetime cigarette smoking history (more than 0 pack-years but no more than 10 pack-years) at the time of the 1985 follow-up examination.

17.5 PNEUMONIA

The prevalence of pneumonia after service in SEA was increased among Ranch Hand enlisted flyers at the 2002 physical examination. No other findings adverse to Ranch Hands or positive associations with dioxin were observed.

17.6 THORAX AND LUNG ABNORMALITY

The occurrence of thorax and lung abnormalities identified at the 1987 follow-up examination increased with dioxin (initial and 1987 levels). At the 1992 follow-up examination, Ranch Hands had a greater prevalence of thorax and lung abnormalities, primarily among enlisted flyers. Ranch Hands in the background dioxin category also had a greater prevalence of thorax and lung abnormalities than Comparisons at this examination.

17.7 HYPERRESONANCE

The prevalence of hyperresonance was elevated among Ranch Hand enlisted flyers at the 1987 follow-up examination. In addition, as 1987 dioxin levels increased in Ranch Hands with early tours of duty, the prevalence of hyperresonance in 1987 increased. No association between hyperresonance and group was found at the 1985 follow-up examination.

17.8 RALES

The prevalence of rales was increased for Ranch Hands in the high dioxin category at the 1987 follow-up examination.

17.9 WHEEZES

The prevalence of wheezes increased as initial dioxin increased for the serum dioxin analysis of the 1987 follow-up report. Analysis in this report also showed the prevalence of wheezes increased as 1987 dioxin increased among older Ranch Hand participants with later tours of duty.

17.10 X-RAY INTERPRETATION

Ranch Hands in the background dioxin category had a higher prevalence of an abnormal chest x-ray interpretation than Comparisons in the analysis of the 1997 follow-up examination.

17.11 FEV₁

For the analysis of data from the 1987 follow-up examination, the average FEV₁ was smaller (adverse effect) in older Ranch Hands than in older Comparisons. Among participants who had never smoked and former smokers, Ranch Hands in the high dioxin category had a smaller average FEV₁ than Comparisons. FEV₁ levels in 1987 decreased as initial and 1987 dioxin levels increased.

17.12 FVC

Similar interaction patterns to those seen for FEV₁ were observed with average FVC levels at the 1987 follow-up examination. Among participants who had never smoked and former smokers, Ranch Hands in the high dioxin category had a smaller average FVC (adverse effect) than Comparisons. FVC levels in 1987 decreased as initial and 1987 dioxin levels increased.

FVC, as measured at the 1992 follow-up examination, decreased as initial dioxin increased. Average FVC levels at the 2002 follow-up examination were smaller for Ranch Hands in the low dioxin category than for Comparisons.

17.13 RATIO OF OBSERVED FEV₁ TO OBSERVED FVC

Ranch Hands in the background dioxin category had a smaller average ratio of FEV₁ to FVC (adverse effect) than Comparisons at the 1987 follow-up examination. This pattern also was observed in older Ranch Hands at the 1992 follow-up examination.

17.14 LOSS OF VITAL CAPACITY

At the 1987 follow-up examination, more Ranch Hands with high levels of 1987 dioxin and later tours of duty had mild losses of vital capacity than did Ranch Hands with low levels of 1987 dioxin and later tours of duty. More Ranch Hands with high levels of 1987 dioxin had mild losses of vital capacity than did Comparisons. In addition, as initial dioxin increased, the risk of a mild loss of vital capacity increased.

At the 1992 follow-up examination, the occurrence of a mild loss of vital capacity in nonsmokers increased as 1987 dioxin increased.

17.15 OBSTRUCTIVE ABNORMALITY

The occurrence of a mild obstructive abnormality was increased for Ranch Hands in the background dioxin category at the 1987 follow-up examination. This same increase was observed at the 1992 follow-up examination for Ranch Hand smokers who were heavy smokers. At the 1997 follow-up examination, the occurrence of a mild obstructive abnormality was increased for Ranch Hand officers.

17.16 CONCLUSION

Patterns that might be expected if there were dioxin or herbicide effects on the pulmonary function, namely consistent results across examinations, an adverse health effect for Ranch Hands or Ranch Hand enlisted groundcrew, and adverse effects to Ranch Hands in the high dioxin category, were not evident. Sporadic and isolated effects were present in many of the endpoints examined, but there was no consistent evidence to suggest that herbicide or dioxin exposure was associated with ill effects on respiratory health.

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18 RENAL ASSESSMENT

18.1 INTRODUCTION

Renal (kidney) dysfunction and overt renal disease are not considered to be important clinical sequelae of exposure to phenoxy herbicides, chlorophenols, or 2,3,7,8-tetrachlorodibenzo-p-dioxin. Both 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), however, are excreted by the kidney as both metabolized and unmetabolized compounds. Therefore, it is consistent that acute renal dysfunction has been reported following acute, high-dose exposure to phenoxy herbicides and dioxin.

Analyses were performed to assess the renal function of Air Force Health Study (AFHS) participants at the 1982, 1985, 1987, 1992, and 2002 examinations (1-6). The renal assessment was based on laboratory data collected at the physical examination, as well as a verified lifetime history of kidney stones and kidney disease, as reported by the participant and subsequently verified by a medical records review.

In the self-administered family and personal history questionnaire, each AFHS participant was asked whether he had ever experienced kidney trouble or kidney stones in the past. A medical records review was accomplished to confirm reported problems with kidney function and to identify any unreported kidney problems. Predominate conditions for past kidney disease included kidney stones, unspecified disorders of the kidney and ureter, and nonspecific findings on the examination of the urine.

Renal variables were quantified by laboratory tests to assess nonspecific renal system function. Urinary protein and urine specific gravity were determined by accepted dipstick methods. Urinary occult blood and urinary white blood cell count were measured by high-powered microscopic examination. Serum creatinine, urinary creatinine, urinary microalbumin, and blood urea nitrogen also were collected and analyzed at selected physical examinations.

18.1.1 Chapter Structure

This chapter is written in a narrative format with the sparse use of statistical significance metrics. Where possible, the discussions are restricted to statistical analyses that have been adjusted for relevant risk and demographic factors. Statistically significant results (p-value of 0.05 or less) are emphasized. Significant results that appeared consistently across examinations or have biological meaning are emphasized, particularly in the Conclusion section of this chapter. Results that are significant, but sporadic, isolated, or inconsistent, are given less emphasis. If an association was found to be adverse to the Comparison group, no mention is made in the chapter. In addition, the results of a nonsignificant association between the parameter and either group or dioxin are not discussed.

The results discussed below that were discovered as part of further analysis based on a statistical interaction may be applicable only for a subgroup of participants (e.g., officers). The subgroup for which the results were found is identified in the description of the analysis. In addition, unless otherwise stated, younger participants were those born in or after 1942, which corresponds to 40 years of age at the baseline examination. Older participants were defined as those born before 1942.

For the 1987 follow-up report based on serum dioxin levels, the number of years between the end of the Ranch Hand's last tour of duty that qualified him for inclusion into the study and the date of the 1987

follow-up examination was calculated. The median difference between the date of the 1987 follow-up examination and the end of the last qualifying tour of duty was 18.6 years. Associations between a health variable and 1987 dioxin were investigated separately for participants whose difference was greater than 18.6 years (referred to as the “earlier” tour of duty throughout this chapter) and whose difference was at most 18.6 years (referred to as the “later” tour of duty throughout this chapter). Further discussion of this stratification based on the participant’s tour of duty is given in Chapter 2.

The following chart lists the variables that were analyzed for the renal assessment and at which physical examination they were analyzed. The variables appearing in bold type are discussed subsequently in the chapter because they showed a statistically significant result adverse to Ranch Hands.

Variable	1982	1985	1987	1987 Serum Dioxin	1992	1997	2002
History of Kidney Stones						Analysis not performed	X
Occurrence of Past Kidney Disease	X	X	X	X	X		X
Blood Urea Nitrogen	X	X	X	X			X
Serum Creatinine					X		X
Creatinine Clearance	X						X
Urinary Microalbumin to Urinary Creatinine Ratio							X
Urine Specific Gravity	X	X	X	X	X		X
Urinary Occult Blood	X	X	X	X	X		X
Urinary White Blood Cells	X	X	X	X	X		X
Urinary Protein	X	X	X		X		X
Kidney Stones from Kidney, Urethra, and Bladder X-ray Assessment					X		
Composite Renal Abnormalities (Blood Urea Nitrogen, Creatinine Clearance, Urinary Occult Blood, Urinary White Blood Cells, Urinary Protein)	X						

18.2 HISTORY OF KIDNEY DISEASE

Answers to the question “Have you ever had kidney disease?” at the 1982 baseline examination showed that Ranch Hands self-reported more kidney disease than Comparisons. At subsequent examinations, affirmative responses to this question were verified by a medical records review.

18.3 SERUM CREATININE

For participants whose glucose levels were considered impaired ($140 \text{ mg/dL} \leq 2\text{-hour postprandial glucose} < 200 \text{ mg/dL}$), more Ranch Hands had a higher average serum creatinine level at the 1992 follow-up examination than Comparisons.

18.4 URINARY OCCULT BLOOD

Black Ranch Hands exhibited a greater percentage of abnormal levels of urinary occult blood (greater than 2 cells per high-powered field) than Black Comparisons at the 1987 follow-up examination. The percentage of abnormal levels of urinary occult blood also increased with increasing initial dioxin at the

1987 follow-up examination. At the 1992 follow-up examination, the prevalence of abnormal levels of urinary occult blood increased with categorized dioxin and 1987 dioxin.

18.5 URINARY WHITE BLOOD CELLS

Younger non-Black Ranch Hands exhibited a greater percentage of abnormal levels of urinary white blood cells (greater than 2 cells per high-powered field) than younger non-Black Comparisons at the 1985 follow-up examination. At the 1992 follow-up examination, the prevalence of abnormal levels of urinary white blood cells was greater for Ranch Hand enlisted groundcrew than for Comparison enlisted groundcrew.

18.6 URINARY PROTEIN

For participants whose glucose levels were considered normal (2-hour postprandial glucose < 140 mg/dL), more Ranch Hands had urinary protein present at the 1985 follow-up examination than did Comparisons.

For participants whose glucose levels were considered impaired ($140 \text{ mg/dL} \leq 2\text{-hour postprandial glucose} < 200 \text{ mg/dL}$), the percentage of Ranch Hands who had urinary protein present at the 1992 follow-up examination increased as the level of 1987 dioxin increased.

18.7 URINE SPECIFIC GRAVITY

Average urine specific gravity levels were greater for non-Black Ranch Hand enlisted groundcrew than for non-Black Comparison enlisted groundcrew at the 1985 follow-up examination. Urine specific gravity levels among older participants increased as initial dioxin increased at the 1992 follow-up examination. Urine specific gravity levels at the 1992 follow-up examination also increased as 1987 dioxin increased.

18.8 CONCLUSION

The AFHS evaluated renal disorders based on medical histories and standard laboratory measures. Throughout the AFHS, the findings of adverse effects or associations with dioxin that were observed appeared to be sporadic and inconsistent across examinations. Many of the relations that were found were present only in subpopulations with no biological basis. The results from the renal assessment indicated no association between any marker of kidney disease and either herbicides or dioxin. In particular, there was no evidence that exposure to herbicides or dioxin was associated with renal dysfunction, kidney stones, prevalence of proteinuria or albuminuria, or cells in the urine.

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19 CONCLUSION

The objective of the Air Force Health Study (AFHS) was to determine whether long-term health effects exist and can be attributed to occupational exposure to herbicides, with specific emphasis on Agent Orange, a one-to-one mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). This report is a discussion and a compilation of the findings from research related to the mortality, reproductive outcomes, and morbidity components of the AFHS.

Congress directed the Secretary of Veterans Affairs in Public Law 102-4 signed on February 6, 1991, to request the National Academy of Sciences to conduct a comprehensive review and evaluation of the available scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used during the Vietnam War. In 1994, the Institute of Medicine (IOM) Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides published its first report, "Veterans and Agent Orange: Health effects of herbicides used in Vietnam." (1) This report classified evidence of an association between a health problem and exposure to herbicides as "sufficient," "limited/suggestive," or "inadequate/insufficient." The evidence regarding association was drawn from occupational, environmental, and veterans studies in which individuals were exposed to the herbicides used in Vietnam, to their components, or to their contaminants. Since this report, the IOM has published five *Veterans and Agent Orange* updates in 1996, 1998, 2000, 2002, and 2004 (2-6), which incorporated results from additional studies.

As a result of the committee's work, the Department of Veterans Affairs has presumed that any veteran who served in Vietnam between January 9, 1962, and May 7, 1975, and has one or more of the following conditions, has been exposed to Agent Orange, and, therefore, his condition is to be considered service-connected: acute and subacute transient peripheral neuropathy (must appear within 1 year of exposure and resolve within 2 years of date of onset); chloracne (must occur within 1 year of exposure); chronic lymphocytic leukemia; Hodgkin's disease; multiple myeloma; non-Hodgkin's lymphoma; porphyria cutanea tarda (must occur within 1 year of exposure); prostate cancer; respiratory cancers, including cancers of the lung, larynx, trachea, and bronchus; soft tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma); spina bifida (in children of Vietnam veterans born after the veteran's tour in Vietnam) (except spina bifida occulta); and type 2 diabetes.

In interpreting results from any epidemiological study, no single result should be evaluated in isolation or out of context. Rather, interpretations should be addressed in the context of the overall study design, the data collection procedures, the data analysis methods, dose-response effects, strength of association, temporal relation, biological plausibility, and internal and external consistency. This especially applies to the AFHS, a large-scale, prospective observational study in which thousands of measurements and diagnoses were compiled on each participant. Those measurements and diagnoses were subjected to extensive statistical analyses, testing thousands of individual hypotheses. Each positive result should be scrutinized relative to findings in other studies, and relative to the statistical methods used and the medical and biological plausibility of the results. Conversely, the lack of a positive result only denotes that the hypothesis of no association was not rejected. This has a very different conclusion than the possibly incorrect assertion that there is no effect. In addition, no epidemiological study can establish that there is no effect; i.e., that dioxin is safe.

In December 1999, the Government Accounting Office (GAO) published the report *Actions Needed to Improve Communications of Air Force Ranch Hand Study Data and Results* (7). This report described the actions needed to improve communications of AFHS data and results to the public. The GAO recommended that more information on the limitations of the AFHS should be communicated in press releases and executive summaries. Below are the strengths and limitations of the study, as determined by AFHS investigators:

Strengths:

- High level of Ranch Hand and Comparison participation
- Existence of a biomarker for exposure to dioxin and herbicides of interest
- Long follow-up period
- Six physical examinations over a 20-year period
- Medical record verification of most health conditions
- Rigorous quality control
- Independently appointment and administered advisory committee (Ranch Hand Advisory Committee)
- Periodic review by the National Academy of Sciences
- Two-tiered management structure based on separate but parallel program management and technical teams
- Adjustment for confounding factors

Limitations:

- Findings cannot be generalized to all Vietnam veterans
- Sample size not adequate to detect small to moderate increases in rare diseases
- Serum dioxin measured over 15 years after Agent Orange exposure
- Possible incomplete adjustment due to unknown confounding factors.

There was no meaningful elevation in risk for spontaneous abortion or stillbirth. There were some elevations in risk in some birth defect organ system categories that were not considered biologically meaningful. There was no indication of increased birth defect severity, delays in development, or hyperkinetic syndrome with paternal dioxin. No association was seen between paternal dioxin level and intrauterine growth retardation. The risk of infant death was increased among children of Ranch Hands whose fathers had the highest dioxin levels and among children whose fathers had background dioxin levels, but the pattern of results implied that the outcomes might not be related to paternal dioxin level. No consistent or meaningful associations between serum dioxin levels and testosterone, follicle-stimulating hormone, luteinizing hormone, testicular abnormalities, and testicular volume were observed.

As of 31 December 1999, 186 Ranch Hands and 2,330 Comparisons had died. The risk of death caused by cancer was not increased, but the risk of death caused by circulatory system diseases was increased in enlisted groundcrew. The cumulative all-cause mortality experience of Ranch Hands was not statistically greater than Comparisons, but this trend bears further monitoring to confirm the increased risk suggested by these results. To examine cancer mortality in a way that accounts for latency, the risk was evaluated among those subjects who survived at least 20 years after entry into follow-up. No differences were

found in this subset, as was also the case with cancer mortality within 20 years of service in Southeast Asia (SEA).

The prevalence of cardiovascular disease does not appear to be associated with dioxin exposure. Abnormal pulses appeared to be related to dioxin in earlier phases of the study, but not in the 2002 follow-up examination. The increase in the number of deaths caused by the diseases of the circulatory system for Ranch Hand nonflying enlisted personnel, however, does point to the possibility of an association with dioxin.

No evidence of chloracne was found. An increased frequency of reported acne after service in SEA in Ranch Hand enlisted groundcrew was observed, but is of uncertain meaning because secondary lesions that were observed revealed no association with herbicide or dioxin exposure.

Results from the 1987, 1992, 1997, and 2002 follow-up examinations showed a consistent and potentially meaningful adverse relation between dioxin levels and diabetes. Although the existence of diabetes was comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism showed the possibility of adverse effects from dioxin in relation to glucose intolerance and insulin production. A dioxin-related increase in severity, a decrease in the time from exposure to first diagnosis, and an increase in fasting glucose and hemoglobin A1c supported the dioxin relation with the occurrence of diabetes. Increased risks of diabetes and diabetic-related measurements were found with initial dioxin, in the high dioxin category, and with 1987 dioxin levels.

Sporadic associations between dioxin levels and thyroid or gonadal hormone abnormalities appeared unlikely to be clinically important.

Analysis of gastrointestinal data indicated that dioxin was associated with hepatic enzymes, such as alanine aminotransferase, aspartate aminotransferase, and gamma glutamyltransferase, and also with lipid-related health indices, such as cholesterol, high-density lipoprotein cholesterol, and triglycerides. Although hepatic enzymes showed an association with dioxin, there was no evidence of an increase in overt liver disease. These findings may represent a dioxin-mediated alteration of biochemical processes or a subtle relation between dioxin and lipid metabolism.

Body mass index was positively associated with 1987 dioxin, possibly reflecting the pharmacokinetics of dioxin elimination.

Increased platelet counts, in addition to the elevated erythrocyte sedimentation rates, may indicate the presence of a chronic inflammatory response to dioxin.

The significant associations between herbicide exposure or dioxin levels and the likelihood of developing cancer were seen primarily for Ranch Hand officers and Ranch Hands in the low dioxin category. Other risk and operational factors discussed in published articles did not show consistent associations in Ranch Hands, but did show some associations in the Comparisons. The AFHS is limited in its ability to detect increases in risks of rare diseases because of the small size of the Ranch Hand population. There was some limited support of an association between dioxin levels and neurological disease related to the peripheral nerves. No consistent associations or clinical evidence, however, appeared to support a relation between dioxin and cranial nerve function or other central nervous system processes.

Although differences between groups and associations with dioxin were seen in the psychological tests performed across the six examinations, no clear patterns were discernible. Differences between Ranch Hands with the highest dioxin levels and Comparisons were seen for tasks involving verbal memory

functioning at the 1982 baseline examination, but these differences were not observed at the 2002 follow-up examination. There does not appear to be any clear evidence of psychological disorders or syndromes that can be associated with exposure to herbicides and dioxin.

There was no evidence of dioxin or herbicide effects on the pulmonary function. Sporadic and isolated effects were present in many of the endpoints examined, but there was no consistent evidence to suggest that either herbicide or dioxin exposure was associated with ill effects on respiratory health.

Throughout the AFHS, the findings of adverse renal effects or associations between renal function and dioxin that were observed appeared to be sporadic and inconsistent across examinations. Many of the relations that were found were present only in subpopulations with no biological basis. The results from the renal assessment indicated no association between any marker of kidney disease and either herbicides or dioxin.

In conclusion, results from the 1987, 1992, 1997, and 2002 follow-up examinations showed a consistent and potentially meaningful adverse relation between dioxin levels and diabetes. Although the existence of diabetes was comparable in Ranch Hands and Comparisons, the assessment of glucose metabolism showed the possibility of adverse effects from dioxin in relation to glucose intolerance and insulin production. In addition, the occurrence of and mortality from diabetes and 11 other conditions that were considered service-connected by the Department of Veterans Affairs because of exposure to herbicides are described in this report for the population of AFHS veterans.

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APPENDIX: ABBREVIATIONS AND ACRONYMS

2,4-D	2,4-dichlorophenoxyacetic acid
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
ADA	American Diabetes Association
AFHS	Air Force Health Study
ALT	alanine aminotransferase
ANA	antinuclear antibody
APP	active pedal plantarflexion
AST	aspartate aminotransferase
ATS	American Thoracic Society
CDC	Centers for Disease Control and Prevention
CMI	Cornell Medical Index
CNS	central nervous system
ECG	electrocardiograph
FEV ₁	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GADA	glutamic acid decarboxylase antibodies
GAO	Government Accounting Office
GGT	gamma glutamyltransferase
HDL	high-density lipoprotein
HLA-DR	human leukocyte antigen-DR
ICD-9-CM	International Classification of Diseases, 9 th Revision, Clinical Modification
Ig	immunoglobulins
IOM	Institute of Medicine
KUB	kidney, urethra, and bladder
LDH	lactate dehydrogenase

LH	luteinizing hormone
MCM	Millon Clinical Multiaxial Inventory
MLC	mixed lymphocyte culture
MMPI	Minnesota Multiphasic Personality Inventory
MSK	mouse stomach kidney
NIOSH	National Institute for Occupational Safety and Health
NKCA	natural killer cell assay
NKCI	natural killer cell assay with Interleukin-2
NCI	National Cancer Institute
PCT	porphyria cutanea tarda
PHA	phytohemagglutinin
ppm	parts per million
ppt	parts per trillion
PSA	prostate-specific antigen
PWM	pokeweed mitogen
RBBB	right bundle branch block
RBC	red blood cell
RVN	Republic of Vietnam
SCL-90-R	Symptom Checklist-90-Revised
SEA	Southeast Asia
SEER	Surveillance, Epidemiology, and End Results
SHBG	sex hormone-binding globulin
T ₃	triiodothyronine
T ₄	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TNF α	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
USAF	United States Air Force
WBC	white blood cell